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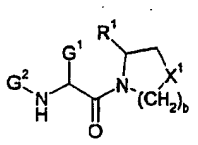
(54) Title: INHIBITORS OF DIPEPTIDYL PEPTIDASE IV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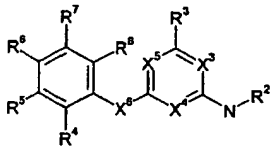
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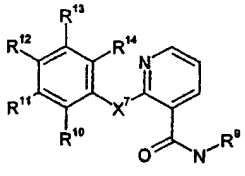
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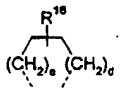
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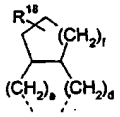
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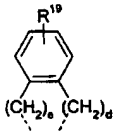
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(57) Abstract: Novel compounds that are inhibitors of one or most post-proline cleaving proteases, e.g. dipeptidyl peptidase IV, according to general formula (1). R^1 is H or CN, X^1 is O, S, CH_2, CHF, CF_2, $CH(CH_3)$, $C(CH_3)_2$ or CH(CN), and b is 1 or 2. G^1 is H or a group according to the formula $-CH_2-X^2-(CH_2)_a-G^3$ and G^2 is H or a group according to the formula $-CH_2-(CH_2)_a-G^3$, provided that one of G^1 and G^2 is H and the other is not H. X^2 is O, S, or CH_2, and a is 0, 1 or 2, provided that when a is 1 then X_2 is CH_2. G^3 is a group according to one of general formulae 2-4., where the variables have meaning given in the description. The compounds are useful in the treatment of i.a. type 2 diabetes and impaired glucose tolerance.

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INHIBITORS OF DIPEPTIDYL PEPTIDASE IV

The present invention relates to novel compounds that are inhibitors of post-proline aminopeptidases. The compounds are useful as antiproliferative agents and in the treatment of, *inter alia*, type 2 diabetes and impaired glucose tolerance.

BACKGROUND

The enzyme dipeptidyl peptidase IV, herein abbreviated DP-IV (and elsewhere as DAP-IV or DPP-IV) and also known by the classification EC.3.4.14.5, is a serine protease that cleaves the N-terminal dipeptide from peptides that begin with the sequence H-Xaa-Pro (where Xaa is any amino acid, although preferably a lipophilic one, and Pro is proline). It will also accept as substrates peptides that begin with the sequence H-Xaa-Ala (where Ala is alanine). DP-IV was first identified as a membrane-bound protein. More recently a soluble form has been identified.

Initial interest in DP-IV focussed on its role in the activation of T lymphocytes. DP-IV is identical to the T cell protein CD26. It was proposed that inhibitors of DP-IV would be capable of modulating T cell responsiveness, and so could be developed as novel immunomodulators. It was further suggested that CD26 was a necessary co-receptor for HIV, and thus that DP-IV inhibitors could be useful in the treatment of AIDS.

Attention was given to the role of DP-IV outside the immune system. It was recognised that DP-IV has a key role in the degradation of several peptide hormones, including growth hormone releasing hormone (GHRH) and glucagon-like peptide-1 and –2 (GLP-1 and GLP-2). Since GLP-1 is known to have a potentiating effect on the action of insulin in the control of post-prandial blood glucose levels it is clear that DP-IV inhibitors might also be usefully employed in the treatment of type II diabetes and impaired glucose tolerance. At least two DP-IV inhibitors are currently undergoing clinical trials to explore this possibility.

Several groups have disclosed inhibitors of DP-IV. While some leads have been found from random screening programs, the majority of the work in this field has been directed towards the investigation of substrate analogues. Inhibitors of DP-IV that are substrate analogues are disclosed in, for example, US 5,462,928, US 5,543,396,

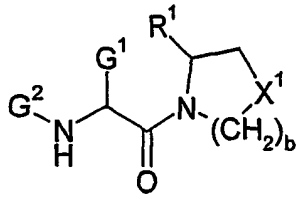
WO95/15309 (equivalent to US 5,939,560 and EP 0731789), WO98/19998 (equivalent to US 6,011,155), WO99/46272 and WO99/61431.

More recently a number of proteins have been found that share some of the enzymatic properties of DP-IV. Some, such as FAP and DPP-8, have sequence homology with DP-IV, while others, such as QPP, have no such homology but nevertheless mimic the aminodipeptidase activity of DP-IV. The physiological function of these newer proteases is still being investigated. FAP has been implicated in invasive processes such as cancer metastasis and endometriosis, and QPP appears to be involved in immune-cell apoptosis. It is also possible that some of these proteases share a common function. This redundancy would allow continuing normal physiological function in the event of a failure in the expression or function of one of the proteases.

In order to further define the roles of these newer proteases it is important to have the tools to manipulate selectively each one or the whole class. Therefore there exists a need for specific and potent inhibitors of each of these proteases, and also for potent non-specific inhibitors of the class of post-proline cleaving aminodipeptidases.

SUMMARY OF THE INVENTION

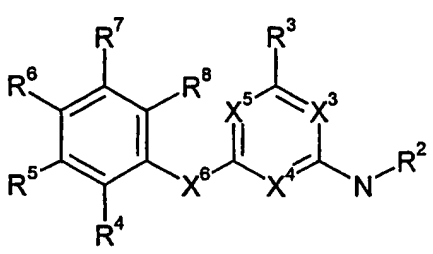
We disclose herein a series of novel compounds that are inhibitors of one or more post-proline cleaving proteases, and specifically compounds according to general formula **1**.



1

In general formula **1**, R^1 is H or CN, X^1 is O, S, CH_2, CHF, CF_2, $CH(CH_3)$, $C(CH_3)_2$ or CH(CN), and b is 1 or 2. G^1 is H or a group according to the formula $-CH_2-X^2-(CH_2)_a-G^3$ and G^2 is H or a group according to the formula $-CH_2-(CH_2)_a-G^3$, provided that one of G^1 and G^2 is H and the other is not H. X^2 is O, S or CH_2, and a is **0**, 1 or 2, provided

that when a is 1 then X^2 is CH_2. G^3 is a group according to one of general formulae **2-4**.



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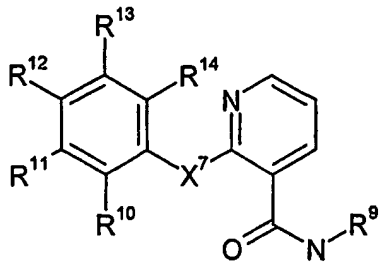

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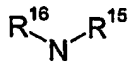
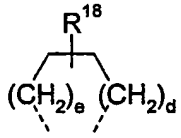


4

X^3, X^4 and X^5 are either nitrogen N or CH, provided that at least two of X^3, X^4 and X^5 are N. X^6 is either O or NH. R^2 is either H or alkyl. R^3 is selected from H, Cl, OH, O-alkyl, NH_2, NH-alkyl and N(alkyl)$_2$. R^4, R^5, R^6, R^7 and R^8 are selected from H, Br, Cl, F, CF_3, alkyl, acyl, OH, O-alkyl, NH_2, NH-alkyl, N(alkyl)$_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, CON(alkyl)$_2$ and CN. X^7 is CH_2, O, S or NH. R^9 is either H or alkyl. R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are selected from H, Br, Cl, F, CF_3, alkyl, acyl, OH, O-alkyl, NH_2, NH-alkyl, N(alkyl)$_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, CON(alkyl)$_2$ and CN. R^{15} and R^{16} are each independently H, alkyl, alkenyl, polyfluoroalkyl, aralkyl, aryl or CH_2-L-R^{17}, where L is a covalent bond, CH=CH, C≡C or -C_6H_4-, and R^{17} is H, alkyl or aryl, or R^{15} and R^{16} together are a group according to one of general formulae **5-7**.



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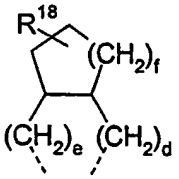

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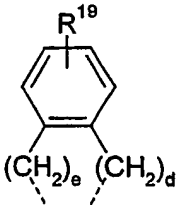


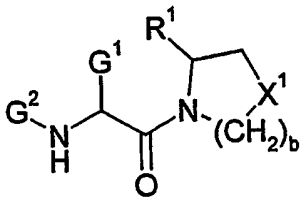
7

R^{18} is H, alkyl, aryl, OH, O-alkyl, NH_2, NH-alkyl or N(alkyl)$_2$, and R^{19} is H, alkyl, aryl, F, Cl, Br, CF_3, OH, O-alkyl, NH_2, NH-alkyl or N(alkyl)$_2$. The integers d and e are 0, 1, 2 or 3 such that d+e is 3, 4 or 5, and f is 1, 2 or 3. When R^{15} and R^{16} are both H then X^1 may not be S or CH_2 if b is 1.

Preferred compositions are inhibitors of non-membrane associated post-proline cleaving proteases. The most preferred compositions are selective for non-membrane associated proteases (e.g. for example inhibitors of one or more of QPP, DPP-8 and/or DPP-9).

DETAILED DESCRIPTION OF THE INVENTION

In a first aspect, the present invention relates to a series of novel α-amino acyl derivatives of saturated nitrogen-containing heterocycles according to general formula **1**.

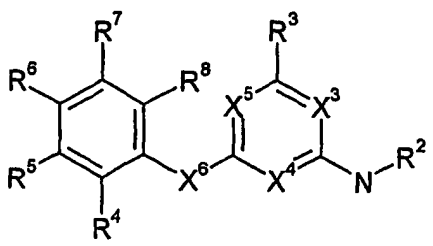


1

In general formula **1**, the group R^1 is either a hydrogen atom H or a nitrile group CN. The group X^1 is selected from an oxygen atom O, a sulphur atom S, a methylene group CH_2, a monofluoromethylene group CHF,a difluoromethylene group CF_2, an ethylidene group $CH(CH_3)$, a 2-propylidene group $C(CH_3)_2$ and a cyanomethylene group CH(CN). The integer b is either 1 or 2, such that the nitrogen-containing ring has 5 or 6 members.

The group G^1 is either H or a group according to the formula $-CH_2-X^2-(CH_2)_a-G^3$ and the group G^2 is either H or a group according to the formula $-CH_2-(CH_2)_a-G^3$, provided that one of G^1 and G^2 is H and the other is not H. The group X^2 is selected from O, S and CH_2. The integer a is **0**, 1 or 2, provided that when a is 1 then X^2 is CH_2.

The group G^3 is selected from a group according to general formula **2**, a group according to general formula **3** and a group according to general formula **4**.



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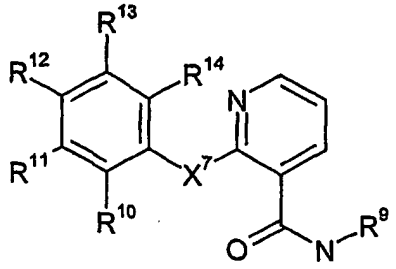

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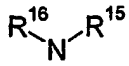
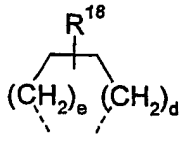


4

In general formula **2**, the groups X^3, X^4 and X^5 are selected from nitrogen N and methine CH, provided that at least two of X^3, X^4 and X^5 are nitrogen. Preferably X^3, X^4 and X^5 are all nitrogen. The group X^6 is selected from O and NH. R^2 is selected from H and alkyl. R^3 is selected from H, Cl, OH, O-alkyl, NH_2, NH-alkyl and N(alkyl)$_2$. R^4, R^5, R^6, R^7 and R^8 are independently selected from H, Br, Cl, F, CF_3, alkyl, acyl, OH, O-alkyl, NH_2, NH-alkyl, N(alkyl)$_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, CON(alkyl)$_2$ and CN.

In general formula **3**, the group X^7 is selected from CH_2, O, S and NH. R^9 is selected from H and alkyl. R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are independently selected from H, Br, Cl, F, CF_3, alkyl, acyl, OH, O-alkyl, NH_2, NH-alkyl, N(alkyl)$_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, CON(alkyl)$_2$ and CN.

In general formula **4**, R^{15} and R^{16} are each independently selected from H, alkyl, alkenyl, polyfluoroalkyl, aralkyl, aryl and CH_2-L-R^{17}, where L is selected from a covalent bond, CH=CH, C≡C and -C_6H_4- and R^{17} is selected from H, alkyl and aryl, or R^{15} and R^{16} together are a group selected from general formula **5**, general formula **6** and general formula **7**.



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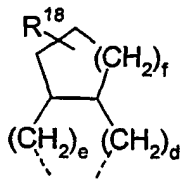

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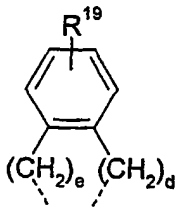


7

In these general formulae, the group R^{18} is selected from H, alkyl, aryl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$, and the group R^{19} is selected from H, alkyl, aryl, F, Cl, Br, CF_3, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$. The integers d and e are selected from 0, 1, 2 and 3 such that d+e is 3, 4 or 5, and the integer f is selected from 1, 2 and 3.

When R^{15} and R^{16} are both H then X^1 may not be S or CH_2 if b is 1.

The term alkyl, as used herein, denotes saturated hydrocarbon groups with between 1 and 10 carbon atoms, including straight-chain, branched and mono- and polycycloalkyl groups, such as methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, cyclopentyl, cyclohexylmethyl, 2-cyclohexyl-2-propyl, bicyclo[2.2.2]octyl and the like.

The term alkenyl, as used herein, denotes monounsaturated hydrocarbon groups with between 2 and 10 carbon atoms, including straight-chain, branched and mono- and polycycloalkenyl groups, such as vinyl, allyl, methallyl, cyclohex-3-enyl and the like.

The term aryl, as used herein, denotes monocyclic and fused bicyclic aromatic groups, including carbocyclic groups, such as phenyl and naphthyl, and heteroaryl groups with up to three heteroatoms selected from nitrogen, oxygen and sulphur, such as pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isothiazolyl, pyridyl, pyrimidinyl, indolyl, quinolinyl and the like. Unless otherwise specified, aryl groups may optionally be substituted with up to three groups independently selected from alkyl, OH, O-alkyl, Cl, F, Br, NH_2, NH-alkyl, $N(alkyl)_2$, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$, NO_2 and CN.

The term aralkyl, as used herein, denotes alkyl groups that are substituted by, or fused to, one or more aryl groups, including benzyl, phenethyl, indanyl, fluorenyl and the like.

The term acyl, as used herein, denotes a group selected from H-CO, alkyl-CO, aryl-CO and aralkyl-CO, including formyl, acetyl, benzoyl, phenylacetyl and the like.

The term polyfluoroalkyl, as used herein, denotes an alkyl group wherein all the hydrogen atoms on one or more of the carbon atoms are replaced by fluorine atoms, including trifluoromethyl, 2,2,2-trifluoroethyl and the like.

In one preferred embodiment of the invention R^1 is H.

In another preferred embodiment of the invention R^1 is CN.

In another preferred embodiment of the invention X^1 is CH_2.

In another preferred embodiment of the invention X^1 is S.

In another preferred embodiment of the invention b is 1.

In another preferred embodiment of the invention b is 2.

In another preferred embodiment of the invention a is 0.

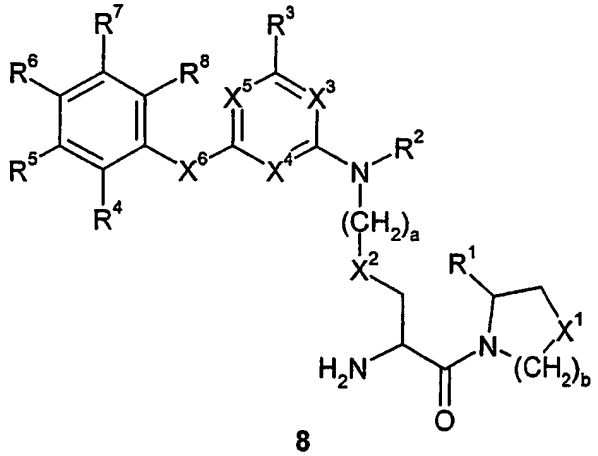
In another preferred embodiment of the invention a is 0 and X^2 is CH_2.

In another preferred embodiment of the invention a is 1.

In another preferred embodiment of the invention a is 1 and X^2 is CH_2.

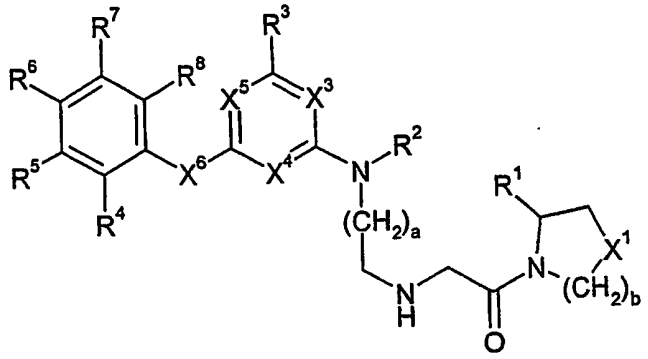
In another preferred embodiment of the invention a is 2 and X^2 is CH_2.

In another preferred embodiment of the invention the compound is a compound according to general formula **8**.



8

In another preferred embodiment of the invention the compound is a compound according to general formula **9**.



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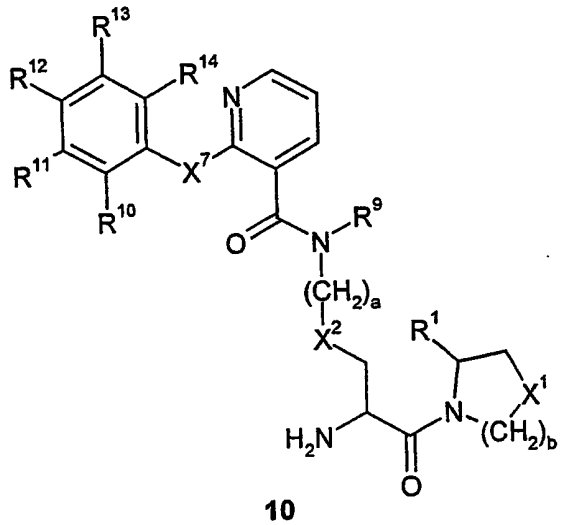
In another preferred embodiment of the invention the compound is a compound according to general formula **10**.



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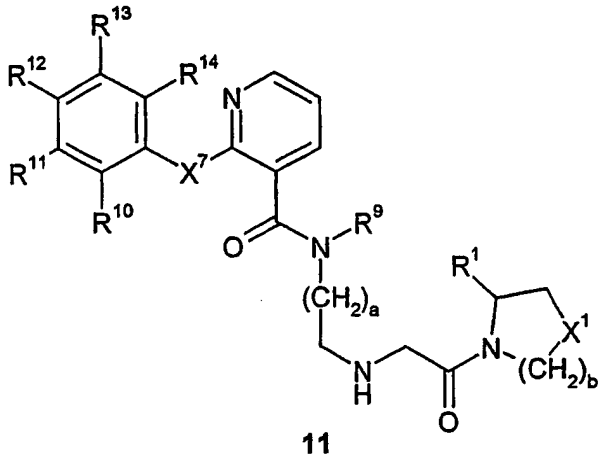
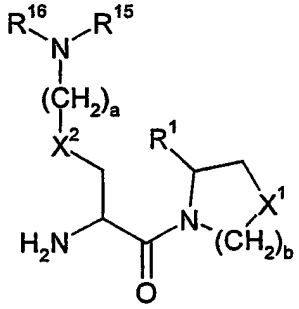
In another preferred embodiment of the invention the compound is a compound according to general formula **11**.



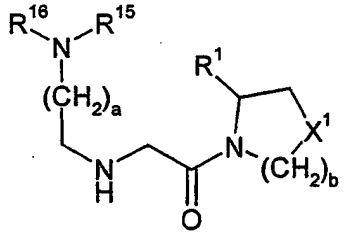
11

In another preferred embodiment of the invention the compound is a compound according to general formula **12**.



12

In another preferred embodiment of the invention the compound is a compound according to general formula **13**.



13

It will be recognised that certain of the compounds within the scope of the present invention are capable of forming salts with suitable acids or bases. To the extent that such salts are pharmaceutically acceptable they are included within the scope of this invention

It will further be recognised that certain of the compounds within the scope of the present invention are capable of existing as optical isomers, such as enantiomers and diastereomers. All such optical isomers and mixtures thereof, including but not limited to racemates, are included within the scope of the invention.

The compounds of the present invention are inhibitors of post-proline cleaving proteases such as DPP-IV, QPP, FAP, DPP-8 (DPRP-1) and DPP-9 (DPRP-2). As such they may be useful in the treatment of diseases in which dysregulation of these enzymes or their endogenous substrates plays a role or the disease is ameliorated by inhibition of such enzymes. Accordingly, in further aspects, the present invention provides for the use of compounds according to the present invention in the preparation of pharmaceutical compositions, and for the use of such compositions a therapeutic agents.

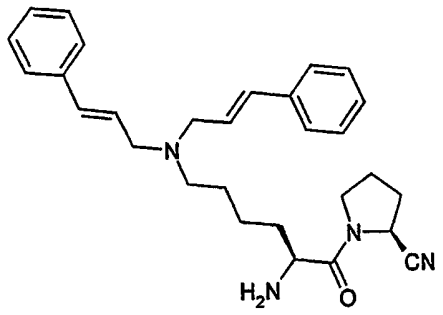
Preferred compositions which are inhibitors for QPP may have G^2=H, b = 1 or 2 and/or a = 0 or 1. Further preferred compositions having b=2 include G1 groups having a=0 or 1 and X^2 is CH_2. Further preferred compositions having b=2 have X^1=CH_2 or S, for example Example 38 of Table 2. Further preferred compositions having b=1 include G1 groups having a=0 or 1 and X^2 is CH_2. . Further preferred compositions having b=1 have X^1= S or CH_2 or CF_2, for example, Example 42 of Table 2.

The compounds of the present invention can be prepared by methods generally known in the art and illustrated in the following non-limiting examples.

EXAMPLES

EXAMPLE 1

(2*S*)-1-[*N*$^{\omega}$,*N*$^{\omega}$-(Dicinnamyl)-L-lysinyl]pyrrolidine-2-carbonitrile dihydrochloride



A. (N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl)-L-prolinamide

N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysine (5g, 10.7mmol) was dissolved in CH_2Cl_2 (100mL). The solution was cooled to 0°C, L-prolinamide (1.78g, 11.7mmol) and PyBOP® (6.7g, 12.8mmol) were added, and the pH adjusted to pH9 with triethylamine. After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (200mL). The solution was washed with 0.3M $KHSO_4$ (2 x 50mL), sat. $NaHCO_3$ (2 x 50mL), water (2 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 2% methanol, 98% chloroform) to give a colourless oil identified as (N^{α}-(*tert*-butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl)-L-prolinamide (4.05g, 7.2mmol, 67%).

B. (2*S*)-1-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl)pyrrolidine-2-carbonitrile

(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl)-L-prolinamide (3.95g, 7.02mmol) was dissolved in dry THF (100mL). The solution was cooled to 0°C, triethylamine (1.4g, 14mmol) was added followed by the slow addition of trifluoroacetic anhydride (2.97g, 14.1mmol). The pH was adjusted to pH9 with triethylamine. After 30min the reaction mixture was diluted with ethyl acetate (100mL), washed with water (1 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo* to give an orange oil. The residue was purified by flash chromatography on silica gel (eluant: 60% pet ether, 40% ethyl acetate) to give a colourless oil identified as (2*S*)-1-(N^{α}-(*tert*-butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl)pyrrolidine-2-carbonitrile (3.3g, 6.11mmol, 87%).

C. (2*S*)-1-(N^{α}-(*tert*-Butyloxycarbonyl)-L-lysinyl)pyrrolidine-2-carbonitrile

(2*S*)-1-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl)-pyrrolidine-2-carbonitrile (3.1g, 5.7mmol) was dissolved in THF (80mL). Diethylamine (20mL) was added. After 2h at room temperature the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a colourless oil identified as (2*S*)-1-(N^{α}-(*tert*-butyloxycarbonyl)-L-lysinyl)pyrrolidine-2-carbonitrile (1.63g, 5.03mmol, 89%).

D. (2*S*)-1-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω},N^{ω}-(dicinnamyl)-L-lysinyl)pyrrolidine-2-carbonitrile

(2*S*)-1-(N^{α}-(*tert*-Butyloxycarbonyl)-L-lysinyl)pyrrolidine-2-carbonitrile (100mg, 0.31mmol) was dissolved in methanol (25mL). To this solution was added trans-cinnamaldehyde (170mg, 1.18mmol). After 30mins sodium triacetoxyborohydride (330mg, 1.56mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 2% methanol, 98% chloroform) to give a colourless oil identified as (2*S*)-1-(N^{α}-(*tert*-butyloxycarbonyl)-N^{ω},N^{ω}-(dicinnamyl)-L-lysinyl)pyrrolidine-2-carbonitrile (38mg, 0.068mmol, 11%). Further elution with 9% methanol, 90% chloroform and 1% acetic acid gave a colourless oil identified as (2*S*)-1-(N^{α}-(*tert*-butyloxycarbonyl)-N^{ω}-(cinnamyl)-L-lysinyl)pyrrolidine-2-carbonitrile (32mg, 0.073mmol, 12%)

E. (2*S*)-1-[N^{ω},N^{ω}-(Dicinnamyl)-L-lysinyl]pyrrolidine-2-carbonitrile dihydrochloride

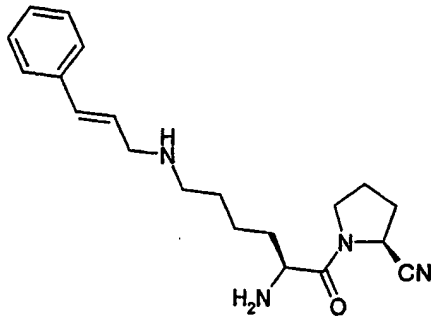
(2*S*)-1-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω},N^{ω}-(dicinnamyl)-L-lysinyl)pyrrolidine-2-carbonitrile (32mg, 0.057mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as (2*S*)-1-[N^{ω},N^{ω}-(dicinnamyl)-L-lysinyl]pyrrolidine-2-carbonitrile dihydrochloride (37mg, 0.053mmol, 93%).

$[M+H]^+ = 457.3$

^1H NMR (CD_3OD): δ 1.35-1.55 (2H, m), 1.75-2.00 (2H, m), 2.05-2.23 (6H, m), 3.10-3.29 (4H, m), 3.61-3.68 (2H, m), 4.00-4.03 (4H, m), 4.20-4.30 (1H, m), 4.82-4.93 (1H, m), 6.34-6.39 (2H, m), 6.94 (2H, d, J = 5.8Hz), 7.31-7.37 (6H, m), 7.39-7.53 (4H, m) ppm.

EXAMPLE 2

(2*S*)-1-[N^{ω}-(Cinnamyl)-L-lysinyl]pyrrolidine-2-carbonitrile dihydrochloride



A. (2*S*)-1-[N^{ω}-(Cinnamyl)-L-lysinyl]pyrrolidine-2-carbonitrile dihydrochloride

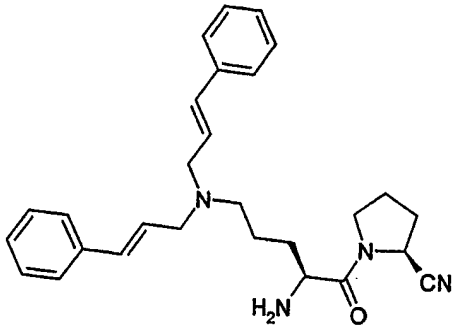
(2*S*)-1-(N^{ω}-(*tert*-Butyloxycarbonyl)-N^{ω}-(cinnamyl)-L-lysinyl)pyrrolidine-2-carbonitrile (32mg, 0.057mmol). was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as (2*S*)-1-[N^{ω}-(cinnamyl)-L-lysinyl]pyrrolidine-2-carbonitrile dihydrochloride (37mg, 0.053mmol, 93%).

$[M+H]^+ = 341.5$

^{1}H NMR (CD_3OD): δ 1.29-1.55 (2H, m), 1.72-1.80 (2H, m), 1.90-2.11 (2H, m), 2.16-2.29 (6H, m), 3.02-3.09 (2H, m), 3.65-3.69 (2H, m), 3.78-3.82 (2H, m), 4.23-4.27 (1H, m), 4.81-4.82 (1H, m), 4.91-4.99 (1H, m), 6.21-6.32 (1H, m), 6.86 (1H, d, J=6.1Hz), 7.26-7.35 (3H, m), 7.37-7.40 (2H, m) ppm.

EXAMPLE 3

(2*S*)-1-[N^{ω},N^{ω}-(Dicinnamyl)-L-ornithinyl]pyrrolidine-2-carbonitrile dihydrochloride



A. (2*S*)-1-(N^{α}-(*tert*-Butyloxycarbonyl)-L-ornithyl)pyrrolidine-2-carbonitrile

(2*S*)-1-(N^{α}-(*tert*-Butyloxycarbonyl)-L-ornithyl)pyrrolidine-2-carbonitrile was prepared by the method described for the lysine derivative in Example 1.

B. (2*S*)-1-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω},N^{ω}-(dicinnamyl)-L-ornithinyl)pyrrolidine-2-carbonitrile

(2*S*)-1-(N^{α}-(*tert*-Butyloxycarbonyl)-L-ornithinyl)pyrrolidine-2-carbonitrile (200mg, 0.65mmol) was dissolved in methanol (25mL). To this solution was added trans-cinnamaldehyde (180mg, 1.25mmol). After 30mins sodium triacetoxyborohydride (343mg, 1.63mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography (eluant: 2% methanol, 98% chloroform) to give a colourless oil identified as (2*S*)-1-(N^{α}-(*tert*-butyloxycarbonyl)-N^{ω},N^{ω}-(dicinnamyl)-L-ornithinyl)-pyrrolidine-2-carbonitrile (77mg, 0.14mmol, 22%). Further elution with 9% methanol, 90% chloroform and 1% acetic acid gave a colourless oil identified as (2*S*)-1-(N^{α}-(*tert*-butyloxycarbonyl)-N^{ω}-(cinnamyl)-L-ornithinyl)pyrrolidine-2-carbonitrile (78mg, 0.18mmol, 28%).

C. (2*S*)-1-[N^{ω},N^{ω}-(Dicinnamyl)-L-ornithinyl]pyrrolidine-2-carbonitrile dihydrochloride

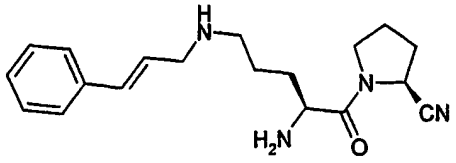
(2*S*)-1-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω},N^{ω}-(dicinnamyl)-L-ornithinyl)pyrrolidine-2-carbonitrile (67mg, 0.12mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as (2*S*)-1-[N^{ω},N^{ω}-(dicinnamyl)-L-ornithinyl]pyrrolidine-2-carbonitrile dihydrochloride (82mg, 0.12mmol, 100%).

$[M+H]^+ = 443.3$

^1H NMR (CD_3OD): δ 1.98-2.12 (4H, m), 2.22-2.29 (4H, m), 3.27-3.31 (4H, m), 3.62-3.67 (2H, m), 3.96 (4H, d, J=7.5Hz), 4.30-4.40 (1H, m), 4.80-4.83 (1H, m), 6.34-6.41 (2H, m), 6.96 (2H, d, J=15.6Hz), 7.31-7.39 (6H, m), 7.49-7.53 (4H, m) ppm.

EXAMPLE 4

(2*S*)-1-[*N*$^{\omega}$-(Cinnamyl)-L-ornithinyl]pyrrolidine-2-carbonitrile dihydrochloride



A. (2*S*)-1-[*N*$^{\omega}$-(Cinnamyl)-L-ornithinyl]pyrrolidine-2-carbonitrile dihydrochloride

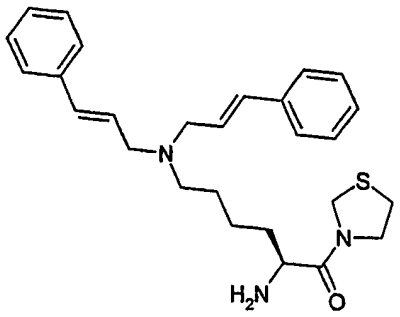
(2*S*)-1-(*N*$^{\alpha}$-(*tert*-Butyloxycarbonyl)-*N*$^{\omega}$-(cinnamyl)-L-ornithinyl)pyrrolidine-2-carbonitrile (71mg, 0.17mmol). was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as (2*S*)-1-[*N*$^{\omega}$-(cinnamyl)-L-ornithinyl]pyrrolidine-2-carbonitrile dihydrochloride (91mg, 0.16mmol, 100%).

$[M+H]^+$ = 327.5

^{1}H NMR (CD_3OD): δ 1.70-1.88 (2H, m), 1.97-2.01 (2H, m), 2.14-2.32 (4H, m), 3.08-3.13 (2H, m), 3.29-3.31 (3H, m), 3.68-3.71 (2H, m), 3.79-3.82 (2H, m), 4.29-4.31 (1H, m), 4.87-4.91 (1H, m), 6.29-6.31 (1H, m), 6.86 (1H, d, J=15.8Hz), 7.29-7.30 (3H, m), 7.44-7.48 (2H, m) ppm.

EXAMPLE 5

3-[*N*$^{\omega}$-*N*$^{\omega}$-(Dicinnamyl)-L-lysinyl]thiazolidine dihydrochloride



A. 3-[N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl]-thiazolidine

N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysine (2.73g, 6mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 100mL). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (1.53g, 10mmol), water-soluble carbodiimide (1.34g, 7mmol), thiazolidine (1.28g, 18mmol) and N-methylmorpholine (1.0g, 10mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100mL). The solution was washed with 0.3M $KHSO_4$ (2 x 25mL), sat. $NaHCO_3$ (2 x 25mL), water (2 x 25mL) and brine (1 x 25mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a white solid identified as 3-[N^{α}-(*tert*-butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl]thiazolidine (2.55g, 4.85mmol, 81%).

B. 3-[N^{α}-(*tert*-Butyloxycarbonyl)-L-lysinyl]thiazolidine

3-[N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl]thiazolidine (1.15g, 2.13mmol) was dissolved in acetonitrile (20mL). Diethylamine (5mL) was added. After 90min at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 3-[N^{α}-(*tert*-butyloxycarbonyl)-L-lysinyl]thiazolidine (530mg, 1.67mmol, 78%).

C. 3-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω},N^{ω}-(dicinnamyl)-L-lysinyl)thiazolidine

3-(N^{α}-(*tert*-Butyloxycarbonyl)-L-lysinyl)thiazolidine (200mg, 0.6mmol) was dissolved in methanol (25mL). To this solution was added trans-cinnamaldehyde (400mg, 3.0mmol). After 30mins sodium triacetoxyborohydride (534mg, 2.54mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 2% methanol, 98% chloroform) to give a colourless oil identified as 3-(N^{α}-(*tert*-butyloxycarbonyl)-N^{ω},N^{ω}-(di-cinnamyl)-L-lysinyl)thiazolidine (139mg, 0.25mmol, 40%).

D. 3-[N^{ω},N^{ω}-(Dicinnamyl)-L-lysinyl]thiazolidine dihydrochloride

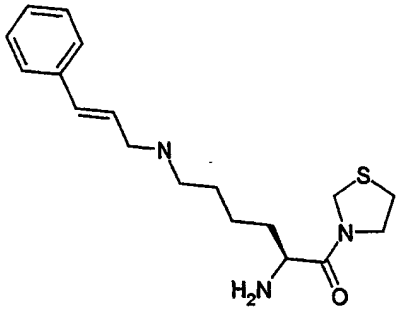
3-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω},N^{ω}-(di-cinnamyl)-L-lysinyl)thiazolidine (139mg, 0.25mmol). was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a pale brown solid identified as 3-[N^{ω},N^{ω}-(dicinnamyl)-L-lysinyl]thiazolidine dihydrochloride (127mg, 0.24mmol, 96%).

$[M+H]^+$ = 450.2

^{1}H NMR (CD_3OD): δ 1.49-1.55 (2H,m), 1.89-1.98 (4H, m), 3.01-3.30 (4H, m), 3.4-3.5 (4H, m), 3.7-3.9 (3H, m), 4.0-4.2 (3H, m), 4.2-4.8 (2H, br m), 6.38-6.44 (2H, m), 6.99-6.93 (2H, m), 7.34-7.37 (5H, m), 7.51-7.60 (4H, m) ppm.

EXAMPLE 6

3-[N^{ω},N^{ω}-(Cinnamyl)-L-lysinyl]thiazolidine dihydrochloride



A. 3-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω},N^{ω}-(cinnamyl)-L-lysinyl)thiazolidine

3-(N^{α}-(*tert*-Butyloxycarbonyl)-L-lysinyl)thiazolidine (200mg, 0.6mmol) was dissolved in methanol (25mL). To this solution was added trans-cinnamaldehyde (400mg, 3.0mmol). After 30mins sodium triacetoxyborohydride (534mg, 2.54mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% triethylamine, 5% methanol, 94% chloroform) to give a colourless oil identified as 3-(N^{α}-(*tert*-butyloxycarbonyl)-N^{ω},N^{ω}-(cinnamyl)-L-lysinyl)thiazolidine (215mg, 0.50mmol, 83%).

B. 3-[N^{ω},N^{ω}-(Cinnamyl)-L-lysinyl]thiazolidine dihydrochloride

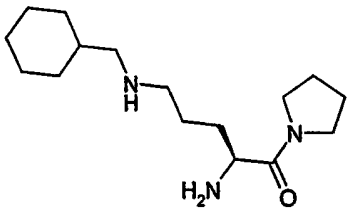
3-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω},N^{ω}-(cinnamyl)-L-lysinyl)thiazolidine (215mg, 0.5mmol). was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a pale brown solid identified as 3-[N^{ω},N^{ω}-(cinnamyl)-L-lysinyl]thiazolidine dihydrochloride (160mg, 0.40mmol, 79%).

$[M+H]^+ = 334.4$

^{1}H NMR (CD_3OD): δ 1.28-1.30 (1H, m), 1.51-1.53 (1H, m), 1.79-1.78 (1H, m), 1.93-1.98 (2H, m), 2.9-3.3 (5H, m), 3.6-3.8 (5H, m), 4.30-4.70 (5H, m), 6.2-6.3 (1H, m), 6.85-6.91(1H, m), 7.1-7.7 (5H, m) ppm.

EXAMPLE 7

1-[N^{ω}-(Cyclohexylmethyl)-L-ornithinyl]pyrolidine dihydrochloride



A. 1-[N^{ω}-(Benzyloxycarbonyl)-N^{α}-(*tert*-butyloxycarbonyl)-L-ornithinyl]pyrrolidine

N^{ω}-(Benzyloxycarbonyl)-N^{α}-(*tert*-butyloxycarbonyl)-L-ornithine (5.49g, 15mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 100mL). To this solution at 0°C was added 1-hydroxybenzotriazole hydrate (3.37g, 22mmol), water-soluble carbodiimide (3.46g, 18mmol), pyrrolidine (1.28g, 18mmol) and N-methylmorpholine (2.0g, 20mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (200mL). The solution was washed with 0.3M $KHSO_4$ (2 x 50mL), sat. $NaHCO_3$ (2 x 50mL), water (2 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 90% ethyl acetate, 10% pet. ether) to give a colourless oil identified as 1-[N^{ω}-(benzyloxycarbonyl)-N^{α}-(*tert*-butyloxycarbonyl)-L-ornithinyl]pyrrolidine (5.15g, 12.3mmol, 82%).

B. 1-[N^{α}-(*tert*-Butyloxycarbonyl)-L-ornithinyl]pyrrolidine

1-[N^{ω}-(Benzyloxycarbonyl)-N^{α}-(*tert*-butyloxycarbonyl)-L-ornithinyl]pyrrolidine (2.15g, 5.13mmol) was dissolved in methanol (80mL). This solution was hydrogenated over 10% Pd/C (400mg). After 2h the catalyst was filtered off and washed with methanol (50mL). The combined filtrates were evaporated *in vacuo* to give an off white solid identified as 1-[N^{α}-(*tert*-butyloxycarbonyl)-L-ornithinyl]pyrrolidine (1.35g, 4.74mmol, 94%).

C. 1-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(cyclohexylmethyl)-L-ornithinyl)pyrrolidine

1-[N^{α}-(*tert*-Butyloxycarbonyl)-L-ornithinyl]pyrrolidine (100mg, 0.35mmol) was dissolved in methanol (25mL). To this solution was added cyclohexanecarboxaldehyde (44mg, 0.39mmol). After 30mins sodium triacetoxyborohydride (148mg, 0.70mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% triethylamine, 5% methanol, 94% chloroform) to give a colourless oil identified as 1-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(cyclohexylmethyl)-L-ornithinyl)pyrrolidine (51mg, 0.18mmol, 52%).

D. 1-[N^{ω}-(Cyclohexylmethyl)-L-ornithinyl]pyrrolidine dihydrochloride

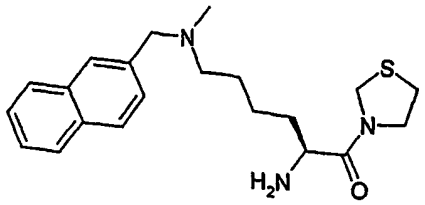
1-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(cyclohexylmethyl)-L-ornithinyl)pyrrolidine (215mg, 0.5mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[N^{ω}-(cyclohexylmethyl)-L-ornithinyl]pyrrolidine dihydrochloride (160mg, 0.40mmol, 79%).

$[M+H]^+ = 282.3$

^1H NMR (CD_3OD): δ 0.93-1.24 (3H, m), 1.66-1.81 (15H, m), 2.50-2.70 (2H, m), 2.71-2.88 (2H, m), 3.2-3.48 (6H, m), 4.08 (1H, m), 8.35-8.38 (1H, m), 8.80-8.85 (1H, m) ppm.

EXAMPLE 8

3-[N^{ω}-Me-N^{ω}-(2-napthylmethyl)-L-lysinyl]thiazolidine dihydrochloride



A. N^{α}-(*tert*-Butyloxycarbonyl-N^{ω}-benzyl-L-lysine methyl ester

N^{α}-(*tert*-Butyloxycarbonyl-L-lysine methyl ester (6.1g, 22.2mmol) was dissolved in methanol (100mL). To this solution was added benzaldehyde (1.9g, 17.5mmol). After 2 hours sodium triacetoxyborohydride (5.8g, 27.3mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (200mL). This solution was washed with sat Na HCO_3 (1 x 50mL), water (12 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid, 5% methanol, 94% chloroform) to give a colourless oil identified as N^{α}-(*tert*-butyloxycarbonyl-N^{ω}- benzyl-L-lysine methyl ester (5.2g, 14.2mmol, 82%).

B. N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-benzyl-N^{ω}-methyl-L-lysine methyl ester

N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-benzyl-L-lysine methyl ester (5.0g, 14.2mmol) was dissolved in methanol (100mL). To this solution was added formaldehyde (37% solution in water, 10mL). After 2 hours sodium triacetoxyborohydride (3.9g, 18.4mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (200mL). This solution was washed with sat. Na HCO_3 (1 x 50mL), water (12 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a . colourless oil identified as N^{α}-*tert*-butyloxycarbonyl- N^{ω}-benzyl-N^{ω}-methyl-L-lysine methyl ester (5.2g, 14.2mmol, 100%).

C. N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-methyl-L-lysine methyl ester

N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-benzyl-N^{ω}-methyl-L-lysine methyl ester (5.0g, 14.2mmol) was dissolved in methanol/water (9:1, 100mL). To this solution was added ammonium formate (1.6, 19.3mmol) and 10% palladium on charcoal (2g) . After 3 hours at 60 ^{0}C the catalyst was filtered off through celite and the residue washed with methanol (50mL). The combined filtrates were evaporated *in vacuo* and the residue was taken up in chloroform (200mL). This solution was washed with sat Na HCO_3 (1 x 50mL),

water (12 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil identified as N^{α}-(*tert*-butyloxycarbonyl-N^{ω}-methyl-L-lysine methyl ester (3.48g, 12.5mmol, 93%).

D. N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-N^{ω}-methyl-L-lysine methyl ester

N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-methyl-L-lysine methyl ester (3.1g, 11.1mmol) was dissolved in dichloromethane (100mL). To this solution was added 1,1-dimethyl-2,2,2-trichloroethyl chloroformate (3.0g, 12.5mmol) and triethylamine (2.3g, 23mmol) . After 18 hours at room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (200mL). This solution was washed with 0.3M $KHSO_4$ (1x 50mL),sat $NaHCO_3$ (1 x 50mL), water (1 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil purified by flash chromatography on silica gel (eluant: 30% ethyl acetate, 70% pet. ether) to give colourless oil identified as N^{α}-(*tert*-butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-N^{ω}-methyl-L-lysine methyl ester (3.28g, 6.98mmol, 63%).

E. N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-N^{ω}-methyl-L-lysine

N^{α}-(*tert*-Butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-N^{ω}-methyl-L-lysine methyl ester (3.1g, 6.6mmol) was dissolved in tetrahydrofuran (100mL). 1M Lithium hydroxide (7mL, 7.0mmol) was added. After 3 hours at room temperature the reaction mixture was diluted with ethyl acetate (150mL), washed with 1M HCl (1 x 50mL), water (1 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo* to give colourless oil identified as N^{α}-(*tert*-butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-N^{ω}-methyl-L-lysine (2.94g, 6.45mmol, 98%).

F. 3-(N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-N^{ω}-methyl-L-lysinyl)thiazolidine

N^{α}-(*tert*-Butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-N^{ω}-methyl-L-lysine (700mg, 1.51mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 20mL). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (410mg, 3.0mmol), water-soluble carbodiimide (250mg, 1.3mmol), thiazolidine (170mg, 1.9mmol) and N-methylmorpholine (1.0g, 10mmol). After 18h at 0°C to room temperature the solvent

was removed *in vacuo* and the residue was taken up in ethyl acetate (70mL). The solution was washed with 0.3M $KHSO_4$ (1 x 25mL), sat. $NaHCO_3$ (1 x 25mL), water (1 x 25mL) and brine (1 x 25mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 50% ethyl acetate, 50% pet. ether) to give a white solid identified as 3-(N^{α}-*tert*-butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-*N*$^{\omega}$-methyl-L-lysinyl)thiazolidine (758mg, 1.42mmol, 94%).

G. 3-(N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-methyl-L-lysinyl)thiazolidine

3-(N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-*N*$^{\omega}$-methyl-L-lysinyl)thiazolidine (730mg, 1.36mmol) was dissolved in acetic acid (30mL). Zinc powder (200mg) was added. After stirring at room temperature for 18 hours the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). The solution was washed with sat. $NaHCO_3$ (1 x 25mL), water (1 x 25mL) and brine (1 x 25mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil identified as 3-(N^{α}-*tert*-butyloxycarbonyl-N^{ω}-methyl-L-lysinyl)thiazolidine (438mg, 1.32mmol, 97%).

H. 3-[N^{α}-*tert*-Butyloxycarbonyl-*N*$^{\omega}$-methyl-N^{ω}-(2-napthylmethyl)-L-lysinyl]thiazolidine

3-(N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-methyl-L-lysinyl)thiazolidine (50mg, 0.15mmol) was dissolved in 1,2-dichloroethane (20mL). To this solution was added 2-naphthaldehyde (26mg, 0.17mmol). After 2 hours sodium triacetoxyborohydride (36mg, 0.17mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 4% methanol, 96% chloroform) to give a colourless oil identified as 3-[N^{α}-*tert*-butyloxycarbonyl-N^{ω}-methyl-*N*$^{\omega}$-(2-napthylmethyl)-L-lysinyl]thiazolidine (51mg, 0.11mmol, 72%).

I. 3-[*N*$^{\omega}$-Methyl-*N*$^{\omega}$-(2-napthylmethyl)-L-lysinyl]thiazolidine dihydrochloride

3-[N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-methyl-*N*$^{\omega}$-(2-napthylmethyl)-L-lysinyl]thiazolidine (44mg, 0.093mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from

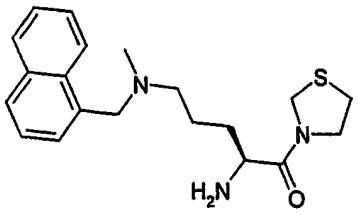
water to give a pale brown solid identified as 3-[N^{ω}-methyl-N^{ω}-(2-napthylmethyl)-L-lysinyl]thiazolidine dihydrochloride (37mg, 0.083mmol, 89%).

$[M+H]^+$ = 372.2

^{1}H NMR (CD_3OD): δ 1.50-1.53 (2H,m), 1.91-1.98 (4H,m), 2.82 (3H,s), 3.08-3.19 (4H,m), 3.36-3.75 (5H,m), 4.32-4.47 (2H,m), 4.60-4.71 (2H,m), 7.55-7.59 (2H,m), 7.65-7.68 (1H,m), 7.90-8.00 (3H,m), 8.10-8.12 (1H,m) ppm.

EXAMPLE 9

3-[N^{ω}-Methyl-N^{ω}-(1-Napthylmethyl)-L-ornithyl]thiazolidine dihydrochloride



A. 3-[*N*-(*tert*-Butyloxycarbonyl)-O^{ω}-methyl-L-glutamyl]thiazolidine

N-(*tert*-Butyloxycarbonyl)-O^{ω}-methyl-L-glutamic acid (6.28g, 24mmol) was dissolved in CH_2Cl_2/DMF (9:1, 100ml). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (5.5g, 36mmol), water-soluble carbodiimide (5.38g, 28mmol), thiazolidine (2.48g, 28mmol) and N-methylmorpholine (3.0g, 30mmol). The mixture was stirred for 18h at 0°C to room temperature then the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (150ml). The solution was washed with 0.3M $KHSO_4$ (2 x 30ml), sat. $NaHCO_3$ (2 x 30ml), water (2 x 30ml) and brine (1 x 30ml), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 70% ethyl acetate, 30% pet. ether 60-80) to give a brown oil identified as 3-[*N*-(*tert*-butyloxycarbonyl)-O^{ω}-methyl-L-glutamyl]thiazolidine (4.0g, 12mmol, 50%).

B. 3-[*N,N*-Di-(*tert*-butyloxycarbonyl)-O^{ω}-methyl-L-glutamyl]thiazolidine

3-[*N*-(*tert*-Butyloxycarbonyl)-O^{ω}-methyl-L-glutamyl]thiazolidine (3.2g, 9.6mmol) was dissolved in acetonitrile (20mL). Di-tert-butyl dicarbonate (3.14g, 14.4mmol) and 4-dimethylaminopyridine (235mg, 1.93mmol) were added. After 18 hours at room temperature further di-tert-butyl dicarbonate (3.14g, 14.4mmol) was added. After a further 3 days at room temperature the solvent was evaporated *in vacuo* the residue was purified by flash chromatography on silica gel (eluant: 70% ethyl acetate, 30% pet.

ether 60-80) to give a colourless oil identified as 3-[*N,N*-di-(*tert*-butyloxycarbonyl)-O^{α}-methyl-L-glutamyl]thiazolidine (2.0g, 4.63mmol, 48%).

C. 3-[*N,N*-Di-(*tert*-butyloxycarbonyl)-L-glutamyl]thiazolidine

3-[*N,N*-di-(*tert*-butyloxycarbonyl)-O^{α}-methyl-L-glutamyl]thiazolidine (950mg, 2.22mmol) was dissolved in THF (50ml). 1M Lithium hydroxide (5.5ml, 5.5mmol) was added. The mixture was stirred for 1 hour at room temperature then the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (70ml). The solution was washed with 0.3M $KHSO_4$ (2 x 20ml), water (2 x 20ml) and brine (1 x 20ml), dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil identified as 3-[*N,N*-di-(*tert*-butyloxycarbonyl)-L-glutamyl]thiazolidine (912mg, 2.2mmol, 98%).

D. 3-[2-(*N,N*-Di-(*tert*-butyloxycarbonyl)amino)-5-hydroxypentanoyl]thiazolidine

3-[*N,N*-Di-(*tert*-butyloxycarbonyl)-L-glutamyl]thiazolidine (912mg, 2.2mmol) was dissolved in tetrahydrofuran (30 mL). This solution was cooled to –20 ^{0}C, N-methylmorpholine (300mg, 2.96mmol) and isobutyl chloroformate (387mg, 2.83mmol) were added. After 20 mins at –20 ^{0}C the reaction mixture was added to a solution of sodium borohydride (182mg, 4.8mmol) in water (5mL) at 0^{0}C. After 1 hour the reaction mixture was diluted with ethyl acetate (150 mL). This solution was washed with water (1 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil identified as 3-[2-(*N,N*-di-(*tert*-butyloxycarbonyl)amino)-5-hydroxy-pentanoyl]thiazolidine (800mg, 2.0mmol, 92%).

E. 3-[2-(*N,N*-Di-(*tert*-butyloxycarbonyl)amino-5-oxopentanoyl]thiazolidine

3-[2-*N,N*-((Di-*tert*-butyloxycarbonyl)amino)-5-hydroxypentanoyl]thiazolidine (800mg, 2.0mmol) was dissolved in dichloromethane (50 mL). Dess-Martin periodinane (933mg,2.2mmol) was added. After 1 hour at room temperature the reaction mixture was diluted with ethyl acetate (150 mL). This solution was washed with water (1 x 20ml) and brine (1 x 20ml), dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil. Purified by flash chromatography on silica gel (eluant: 50% ethyl acetate, 50% pet. ether 60-80) to give a colourless oil identified as 3-[2-(*N,N*-di-(*tert*-butyloxycarbonyl)amino-5-oxopentanoyl]thiazolidine (210mg, 0.52mmol, 26%).

F. 3-[*N,N*-Di-(*tert*-butyloxycarbonyl-*N*$^{\omega}$-methyl-*N*$^{\omega}$-(1-napthylmethyl)-L-ornithyl]-thiazolidine

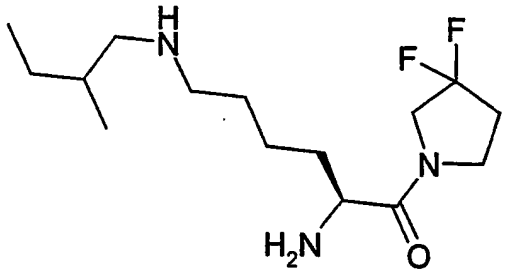
3-[*N,N*-Di-(*tert*-butyloxycarbonyl)amino-5-oxopentanoyl]thiazolidine was dissolved in 1,2-dichloroethane (20mL). To this solution was added N-methyl-1-napthylmethylamine. After 2 hours sodium triacetoxyborohydride was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel to give a colourless oil identified as 3-[*N,N*-di-(*tert*-butyloxycarbonyl-*N*$^{\omega}$-methyl-*N*$^{\omega}$-(1-napthylmethyl)-L-ornithyl]thiazolidine.

G. 3-[*N*$^{\omega}$-Methyl-*N*$^{\omega}$-(1-Napthylmethyl)-L-ornithyl]thiazolidine dihydrochloride

3-[*N,N*-Di-(*tert*-butyloxycarbonyl-*N*$^{\omega}$-methyl-*N*$^{\omega}$-(1-napthylmethyl)-L-ornithyl]thiazolidine was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a pale brown solid identified as 3-[*N*$^{\omega}$-Me,*N*$^{\omega}$-(1-napthylmethyl)-L-ornithyl]thiazolidine dihydrochloride.

EXAMPLE 10

3,3-Difluoro-1-[*N*$^{\omega}$-(2-methylbutyl)-L-lysinyl]pyrrolidine dihydrochloride



A. 1-(*tert*-Butyloxycarbonyl)-3-pyrrolidone

(3*R*)-1-(*tert*-Butyloxycarbonyl)-3-hydroxypyrrolidine (980mg, 5.3mmol) was dissolved in CH_2Cl_2 (40ml). Dess-Martin periodinane (2.5g, 5.8mmol) was added. The mixture was stirred for 3 hours at room temperature then the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (300ml). The solution was washed with sat. $NaHCO_3$, water and brine, dried (Na_2SO_4) and evaporated *in vacuo* to give a

colourless oil. The residue was purified by flash chromatography on silica gel (eluant: 20% ethyl acetate, 80% pet. ether 60-80) to give a colourless oil identified as 1-(*tert*-butyloxycarbonyl)-3-pyrrolidone (842mg, 4.6mmol, 87%).

B. 1-(*tert*-Butyloxycarbonyl)-3,3-difluoropyrrolidine

1-(*tert*-Butyloxycarbonyl)-3-pyrrolidone (810mg, 4.4mmol) was dissolved in CH_2Cl_2 (30ml). (Diethylamino)sulphur trifluoride (2.2g, 13.7mmol) was added to this solution at 0°C. The mixture was stirred for 18 hours at 0°C to room temperature then carefully poured into sat. $NaHCO_3$ (100ml). The mixture was stirred for 15min then extracted with CH_2Cl_2. The organic extract was washed with water and brine, dried (Na_2SO_4) and evaporated *in vacuo* to give an orange oil. The residue was purified by flash chromatography (eluant: 10% ethyl acetate, 90% pet. ether 60-80) to give a colourless oil identified as 1-(*tert*-butyloxycarbonyl)-3,3-difluoropyrrolidine (580mg, 2.8mmol, 64%).

C. 3,3-Difluoropyrrolidine hydrochloride

1-(*tert*-Butyloxycarbonyl)-3,3-difluoropyrrolidine (540mg, 2.6mmol) was dissolved in 4M HCl/dioxan (30ml). The solution was stirred for 1 hour at room temperature then the solvent was removed *in vacuo* to give an off white solid identified as 3,3-difluoropyrrolidine hydrochloride (370mg, 2.6mmol, 100%).

D. 1-[N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl]-3,3-difluoropyrrolidine

N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysine (1.14g, 2.4mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 100ml). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (394mg, 2.9mmol), water-soluble carbodiimide (680mg, 3.4mmol), 3,3-difluoropyrrolidine hydrochloride (380mg, 2.43mmol) and N-methylmorpholine (400mg, 4mmol). The mixture was stirred for 18h at 0°C to room temperature then the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (200ml). The solution was washed with 0.3M $KHSO_4$, sat. $NaHCO_3$, water and brine, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 65% ethyl acetate, 35% pet. ether 60-80) to give a white solid identified as 1-[N^{α}-(*tert*-butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl]-3,3-difluoropyrrolidine (1.0g, 1.8mmol, 75%).

E. 1-[N^{α}-(*tert*-Butyloxycarbonyl)-L-lysinyl]-3,3-difluoropyrrolidine

1-[N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl]-3,3-difluoropyrrolidine (1.01g, 1.8mmol) was dissolved in THF (20ml). Diethylamine (5ml) was added. The mixture was stirred for 3 hours at room temperature then the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 1-[N^{α}-(*tert*-butyloxycarbonyl)-L-lysinyl]-3,3-difluoropyrrolidine (598mg, 1.78mmol, 99%).

F. 1-[N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(2-methylbutyl)-L-lysinyl]-3,3-difluoropyrrolidine

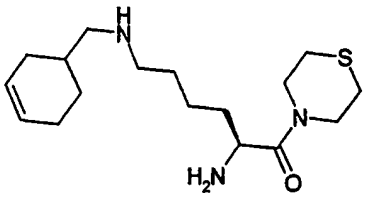
1-[N^{α}-(*tert*-Butyloxycarbonyl)-L-lysinyl]-3,3-difluoropyrrolidine was dissolved in 1,2-dichloroethane (20mL). To this solution was added 2-methylbutanal. After 2 hours sodium triacetoxyborohydride was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel to give a colourless oil identified as 1-[N^{α}-(*tert*-butyloxycarbonyl)-N^{ω}-(2-methylbutyl)-L-lysinyl]-3,3-difluoropyrrolidine.

G. 3,3-Difluoro -1-[N^{ω}-(2-methylbutyl)-L-lysinyl] pyrrolidine dihydrochloride

1-[N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(2-methylbutyl)-L-lysinyl]-3,3-difluoropyrrolidine was dissolved in 4M HCl/dioxan (20ml). The mixture was stirred for 1 hour at room temperature then the solvent was removed *in vacuo* to give a colourless oil identified as 3,3-difluoro-1-[N^{ω}-(2-methylbutyl)-L-lysinyl]pyrrolidine dihydrochloride.

EXAMPLE 11

1-[N^{ω}-(3-Cyclohexenylmethyl)-L-lysinyl]thiomorpholine dihydrochloride



A. 3-[N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl]thiomorpholine

N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysine (2.5g, 5.34mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 100mL). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (1.44g, 10.6mmol), water-soluble carbodiimide (1.35g, 6.5mmol), thiomorpholine (710mg, 6.9mmol) and N-methylmorpholine (800mg, 8mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100mL). The solution was washed with 0.3M $KHSO_4$ (2 x 25mL), sat. $NaHCO_3$ (2 x 25mL), water (2 x 25mL) and brine (1 x 25mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a white solid identified as 3-[N^{α}-(*tert*-butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl]thiomorpholine (2.70g, 4.88mmol, 91%).

B. 3-[N^{α}-(*tert*-Butyloxycarbonyl)-L-lysinyl]thiomorpholine

3-[N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl]thiomorpholine (2.6g, 4.7mmol) was dissolved in tetrahydrofuran (20mL). Diethylamine (5mL) was added. After 90min at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 3-[N^{α}-(*tert*-butyloxycarbonyl)-L-lysinyl]thiomorpholine (1.2g, 3.637mmol, 77%).

C. 3-[N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(3-cyclohexenylmethyl)-L-lysinyl]-thiomorpholine

3-(N^{α}-(*tert*-Butyloxycarbonyl)-L-lysinyl)thiomorpholine (150mg, 0.45mmol) was dissolved in methanol (25mL). To this solution was added 3-cyclohexenecarboxaldehyde (400mg, 0.45mmol). After 30mins sodium triacetoxyborohydride (150mg, 0.71mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid,9% methanol, 90% chloroform) to give a colourless oil identified as 3-(N^{α}-(*tert*-butyloxycarbonyl)-N^{ω}-(3-cyclohexenylmethyl)-L-lysinyl)thiomorpholine (66mg, 0.12mmol, 26%).

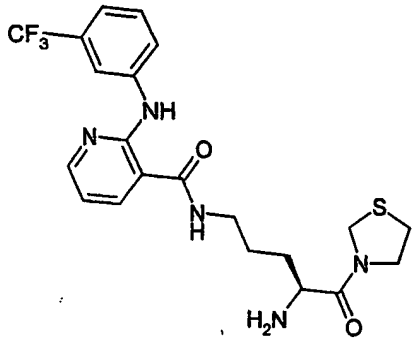
D. 1-[N^{ω}-(3-Cyclohexenylmethyl)-L-lysinyl]thiomorpholine dihydrochloride

3-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(3-cyclohexenylmethyl)-L-lysinyl)thiomorpholine (66mg, 0.12mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[N^{ω}-(3-cyclohexenylmethyl)-L-lysinyl]thiomorpholine dihydrochloride (62mg, 0.12mmol, 100%).

$[M+H]^+ = 326.2$

EXAMPLE 12

(2*S*)-1-[N^{ω}-(2-(3'-trifluoromethylanilino)pyridyl-3-carbonyl)-L-ornithyl]thiazolidine dihydrochloride



A. 3-[N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-L-ornithyl]thiazolidine

N^{α}-(*tert*-Butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-L-ornithine (2.5g, 5.9mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 30mL). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (1.6g, 11.9mmol), water-soluble carbodiimide (1.4g, 7.6mmol), thiazolidine (650mg, 7.3mmol) and N-methylmorpholine (2.0g, 20mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (70mL). The solution was washed with 0.3M $KHSO_4$ (1 x 25mL), sat. $NaHCO_3$ (1 x 25mL), water (1 x 25mL) and brine (1 x 25mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 70% ethyl acetate, 30% pet. ether) to

give a colourless oil identified as 3-[N^{α}-*tert*-butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-L-ornithyl]thiazolidine (758mg, 1.42mmol, 94%).

B. 3-(N^{α}-*tert*-Butyloxycarbonyl- L-ornithinyl)thiazolidine

3-[N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-L-ornithyl]thiazolidine (130mg, 0.26mmol) was dissolved in acetic acid (30mL). Zinc powder (100mg) was added. After stirring at room temperature for 18 hours the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). The solution was washed with sat. $NaHCO_3$ (1 x 25mL), water (1 x 25mL) and brine (1 x 25mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil identified as 3-(N^{α}-*tert*-butyloxycarbonyl-L-ornithinyl)thiazolidine (80mg, 0.26mmol, 100%).

C. 3-[N^{α}-*tert*-Butyloxycarbonyl-*N*$^{\omega}$-(2-(3'-trifluoromethylanilino)pyridyl-3-carbonyl)-L-ornithinyl]thiazolidine

3-(N^{α}-*tert*-Butyloxycarbonyl-L-ornithinyl)thiazolidine (80mg, 0.26mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 20mL). To this solution at 0°C was added 1-hydroxybenzotriazole hydrate (80mg, 0.6mmol), water-soluble carbodiimide (65mg, 0.32mmol), niflumic acid (82mg, 0.29mmol) and N-methylmorpholine (100mg, 1.0mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (70mL). The solution was washed with 0.3M $KHSO_4$ (1 x 20mL), sat. $NaHCO_3$ (1 x 20mL), water (1 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a yellow oil identified as 3-[N^{α}-*tert*-butyloxycarbonyl-*N*$^{\omega}$-(2-(3'-trifluoromethylanilino)pyridyl-3-carbonyl)-L-ornithinyl]-thiazolidine (60mg, 0.12mmol, 45%).

D. (2*S*)-1-[*N*$^{\omega}$-(2-(3'-Trifluoromethylanilino)pyridyl-3-carbonyl)-L-ornithyl]-thiazolidine dihydrochloride

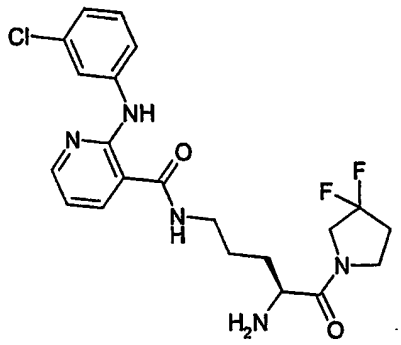
3-[N^{α}-*tert*-Butyloxycarbonyl-*N*$^{\omega}$-(2-(3'-trifluoromethylanilino)pyridyl-3-carbonyl)-L-ornithinyl]thiazolidine (54mg, 0.10mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a pale brown solid identified as (2*S*)-1-[*N*$^{\omega}$-(2-(3'-trifluoromethylanilino)pyridyl-3-carbonyl)-L-ornithyl]thiazolidine dihydrochloride (47mg, 0.10mmol, 100%).

$[M+H]^+$ = 468.0

^{1}H NMR (CD_3OD): δ1.77-1.82 (2H, m), 1.84-2.00 (2H, m), 3.03-3.15 (4H, m), 3.41-3.51 (2H, m), 3.65-3.71 (2H, m), 3.80-3.87 (1H, m), 4.46-4.49 (2H, m), 4.65-4.72 (2H, m), 7.06-7.11 (1H, m), 7.61-7.11 (3H, m), 7.95 (1H, s), 8.09 (1H, d, J=4.7Hz), 8.49 (1H, d, J= 4.2Hz) ppm.

EXAMPLE 13

3,3-Difluoro-1-[*N*$^{\omega}$-(2-(3'-chloroanilino)pyridyl-3-carbonyl)-L-ornithyl]pyrrolidine dihydrochloride



A. 1-[*N*$^{\alpha}$-(*tert*-Butyloxycarbonyl)-L-ornithyl]-3,3-difluoropyrrolidine

1-[*N*$^{\alpha}$-(*tert*-Butyloxycarbonyl)-L-ornithyl]-3,3-difluoropyrrolidine was prepared as described for the lysine derivative in Example 9.

B. 3-Chloroanilinonicotinic acid

3-Chloroaniline was dissolved in xylene. 2-Aminonicotinic acid was added. The reaction mixture was heated at 150 ^{0}C for 18 hours after which time the reaction mixture was diluted with ethyl acetate giving an off-white solid identified as 3-chloroanilinonicotinic acid.

C. 3,3-Difluoro-[N$^{\alpha}$-*tert*-butyloxycarbonyl-*N*$^{\omega}$-(2-(3'-chloroanilino)pyridyl-3-carbonyl)-L-ornithinyl]pyrrolidine

1-[*N*$^{\alpha}$-(*tert*-Butyloxycarbonyl)-L-ornithyl]-3,3-difluoropyrrolidine was dissolved in CH_2Cl_2 /DMF (9:1, 20mL). To this solution at 0°C was added 1-hydroxybenzotriazole hydrate, water-soluble carbodiimide, 3-chloroanilinonicotinic acid and N-methylmorpholine.

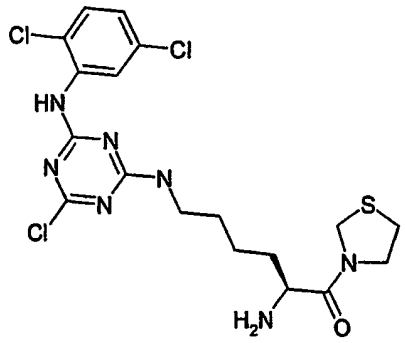
After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (70mL). The solution was washed with 0.3M $KHSO_4$ (1 x 20mL), sat. $NaHCO_3$ (1 x 20mL), water (1 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a yellow oil identified as 3,3-difluoro-[N^{α}-*tert*-butyloxycarbonyl-N^{ω}-(2-(3'-chloroanilino)pyridyl-3-carbonyl)]-L-ornithinyl)pyrrolidine.

D. 3,3-Difluoro-1-[N^{ω}-(2-(3'-chloroanilino)pyridyl-3-carbonyl)-L-ornithyl]pyrrolidine dihydrochloride

3,3-Difluoro-[N^{α}-*tert*-butyloxycarbonyl-N^{ω}-(2-(3'-chloroanilino)pyridyl-3-carbonyl)]-L-ornithinyl)pyrrolidine was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a pale brown solid identified as 3,3-difluoro-1-[N^{ω}-(2-(3'-chloroanilino)pyridyl-3-carbonyl)-L-ornithyl]pyrrolidine dihydrochloride.

EXAMPLE 14

3-[N^{ω}-6-Chloro-4-(2',5'-dichloroanilino)-1,3,5-triazinyl)-L-lysinyl]thiazolidine dihydrochloride



A. 4,6-Dichloro-2-(2',5'-dichloroanilino)-1,3,5-triazine

Cyanuric chloride (1.844g, 10mmol) was dissolved in acetonitrile (20mL). The solution was cooled to –20 °C. A solution of 2,5-dichloroaniline (1.62g, 10mmol) and triethylamine (1.0g, 10mmol) was slowly added. After 1 hour at –20 °C the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (150mL). The

solution was washed with water (1 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was recrystallised from ethyl acetate/ hexane to give an off white solid identified as 4,6-dichloro-2-(2',5'-dichloroanilino)-1,3,5-triazine (1.86mg, 6.0mmol, 60%).

B. 3-[N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-6-chloro-4-(2',5'-dichloroanilino)-1,3,5-triazinyl)-L-lysinyl]thiazolidine

3-(N^{α}-(*tert*-Butyloxycarbonyl)-L-lysinyl)thiazolidine (800mg, 2.58mmol) was dissolved in dichloromethane (30mL). To this solution was added 4,6-dichloro-2-(2',5'-dichloroanilino)-1,3,5-triazine (810mg, 2.6mmol) and triethylamine (300mg, 3.0mmol). After 2 hours at room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (150mL). This solution was washed with water (2 x 30mL) and brine (1 x 30mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography (eluant: 60% ethyl acetate, 40% pet. ether) to give a white solid identified as 3-[N^{α}-*tert*-butyloxycarbonyl-N^{ω}-6-chloro-4-(2',5'-dichloroanilino)-1,3,5-triazinyl)-L-lysinyl]thiazolidine (1.33g, 2.23mmol, 86%).

C. 3-[N^{ω}-6-Chloro-4-(2',5'-dichloroanilino)-1,3,5-triazinyl)-L-lysinyl]thiazolidine dihydrochloride

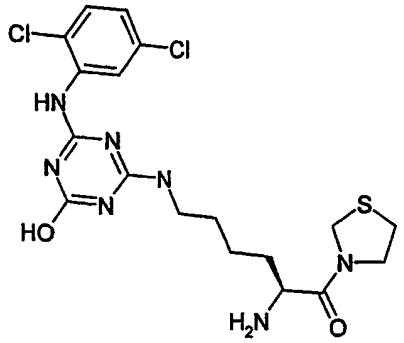
3-[N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-6-chloro-4-(2',5'-dichloroanilino)-1,3,5-triazinyl)-L-lysinyl]thiazolidine (59mg, 0.10mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 3-[N^{ω}-6-chloro-4-(2',5'-dichloroanilino)-1,3,5-triazinyl)-L-lysinyl]thiazolidine dihydrochloride (55mg, 0.098mmol, 98%).

$[M+H]^+$ = 492.2, 494.4

^1H NMR (CD_3OD): δ1.46-1.51 (2H,m), 1.65--1.67 (2H,m), 1.80-1.96 (2H,m), 3.05-3.14 (2H,m), 3.38-3.42 (2H,m), 3.55-3.75 (4H,m), 4.31-4.36 (2H,m0, 4.40-4.52 (1H,m), 4.63-4.95 (2H,m), 7.15-7.18 (1H,m), 7.40-7.45 (1H,m), 8.15-8.25 (1H,m) ppm.

EXAMPLE 15

3-[N^{ω}-4-(2',5'-Dichloroanilino)-6-hydroxy-1,3,5-triazinyl)-L-lysinyl]thiazolidine bis(trifluoroacetate)



A. 3-[N^{ω}-4-(2',5'-Dichloroanilino)-6-hydroxy-1,3,5-triazinyl)-L-lysinyl]thiazolidine bis(trifluoroacetate)

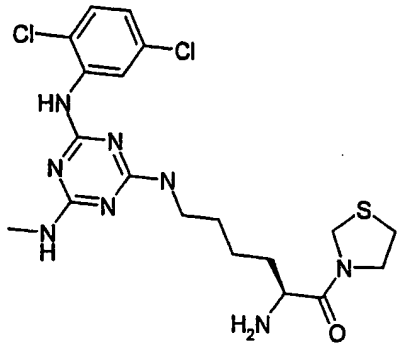
3-[N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-6-chloro-4-(2',5'-dichloroanilino)-1,3,5-triazinyl)]-L-ornithinyl)thiazolidine (54mg, 0.09mmol) was dissolved in trifluoroacetic acid (20mL) and water (2mL). After 2 hours at 70 ^{0}C the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 3-[N^{ω}-4-(2',5'-dichloroanilino)-6-hydroxy-1,3,5-triazinyl)-L-lysinyl]thiazolidine bis(trifluoroacetate) (63mg, 0.089mmol, 97%).

$[M+H]^{+}$ = 472.1, 474.2

^{1}H NMR (CD_3OD): δ1.42-1.47 (2H,m), 1.62-1.67 (2H,m), 1.82-1.89 (2H,m), 3.04-3.16 (4H,m), 3.70-3.75 (2H,m), 3.84-3.91 (1H,m), 4.25-4.32 (2H,m), 4.45-4.54 (2H,m), 4.64-4.70 (2H,m), 7.05-7.15 (1H,m), 7.34-7.38 (1H,m), 7.49-7.55 (1H,m), 7.80-7.92 (1H,m) ppm.

EXAMPLE 16

3-[N^{ω}-4-(2',5'-Dichloroanilino)-6-methylamino-1,3,5-triazinyl)-L-lysinyl]thiazolidine dihydrochloride



A. 3-[N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-4-(2',5'-dichloroanilino)-6-dimethylamino-1,3,5-triazinyl)-L-lysinyl]thiazolidine

3-[N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-3-chloro-5-(2',5'-dichloroanilino)-2,4,6-triazinyl)]-L-ornithinyl)thiazolidine (120mg, 0.20mmol) was dissolved in 1M dimethylamine in tetrahydrofuran (25mL). After 18 hours at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 70% ethyl acetate, 30% pet. ether) to give a white solid identified as 3-[N^{α}-*tert*-butyloxycarbonyl-N^{ω}-4-(2',5'-dichloroanilino)-6-dimethylamino-1,3,5-triazinyl)-L-lysinyl]thiazolidine (110mg, 0.18mmol, 90%).

B. 3-[N^{ω}-4-(2',5'-Dichloroanilino)-6-dimethylamino-1,3,5-triazinyl)-L-lysinyl]-thiazolidine dihydrochloride

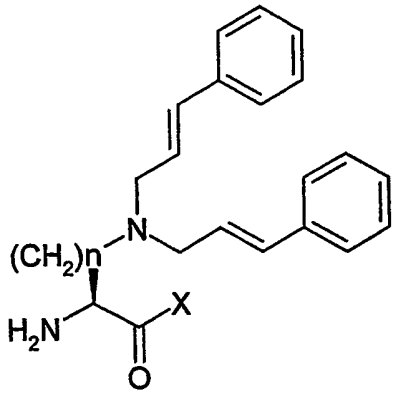
3-[N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-4-(2',5'-dichloroanilino)-6-dimethylamino-1,3,5-triazinyl)-L-lysinyl]thiazolidine (110mg, 0.18mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 3-[N^{ω}-4-(2',5'-dichloroanilino)-6-dimethylamino-1,3,5-triazinyl)-L-lysinyl]thiazolidine dihydrochloride (105mg, 0.18mmol, 100%).

$[M+H]^+$ = 499.1, 501.1

^{1}H NMR (CD_3OD): δ1.52-1.55 (2H,m), 1.69-1.71 (2H,m), 1.90-1.98 (2H,m), 3.13-3.22 (8H,m), 3.48-3.62 (2H,m), 3.65-3.69 (4H,m), 4.37-4.39 (2H,m), 4.46-4.49 (1H,m), 4.57-4.77 (2H,m), 7.20-7.22 (1H,m), 7.45-7.50 (1H,m), 8.09-8.12 (1H,m) ppm.

The following compounds were prepared by analogous methods.

TABLE 1



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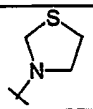
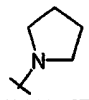
17	3		22	3	
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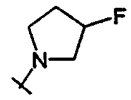
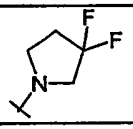
18	3		24	3	
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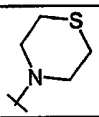
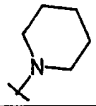
20	3		26	3	
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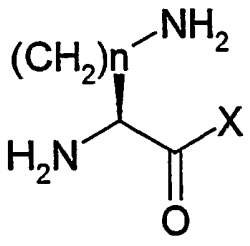

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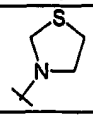
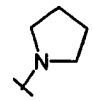
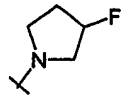
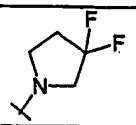
28	2		41	2	
29	2		42	2	
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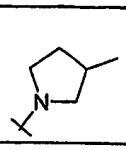
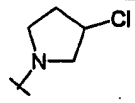
32	2		46	2	
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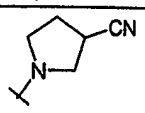
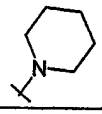
35	2		49	2	
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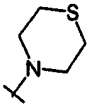
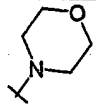
38	2		50	2	
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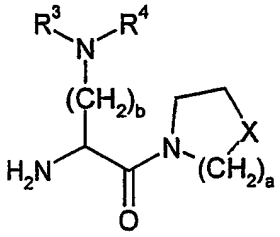
TABLE 3



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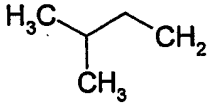
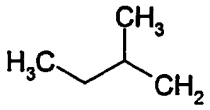
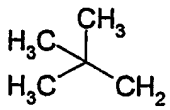
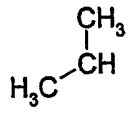
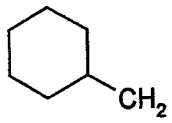
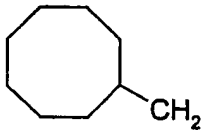
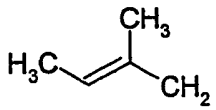
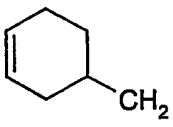
55	1	3	CH_2	H	
56	1	4		H	
57	1	3	CF_2	H	
58	1	4		H	
59	1	4	S	CH_3	
60	1	4		$CH(CH_3)_2$	
61	1	4	CH_2	CH_3	
62	1	4		$CH(CH_3)_2$	

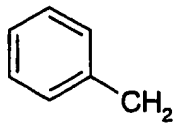
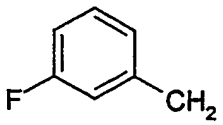
Ex No	a	b	X	R^3	R^4
63	1	3	S	$CH(CH_3)_2$	
64	1	3	CH_2	$CH(CH_3)_2$	
65	2	3	S	H	
66	2	4		H	
67	2	3	CH_2	H	
68	2	4		H	
69	1	3	S	H	
70	1	4		H	
71	1	3	CH_2	H	
72	1	4		H	
73	1	3	CF_2	H	
74	1	4		H	
75	1	4	S	CH_3	
76	1	4		$CH(CH_3)_2$	
77	1	4	CH_2	CH_3	
78	1	4		$CH(CH_3)_2$	
79	1	3	S	$CH(CH_3)_2$	
80	1	3	CH_2	$CH(CH_3)_2$	
81	2	3	S	H	
82	2	4		H	
83	2	3	CH_2	H	
84	2	4		H	
85	1	3	S	H	
86	1	4		H	
87	1	3	CH_2	H	
88	1	4		H	
89	1	3	CF_2	H	
90	1	4		H	
91	1	4	S	CH_3	
92	1	4		$CH(CH_3)_2$	
93	1	4	CH_2	CH_3	
94	1	4		$CH(CH_3)_2$	
95	1	3	S	$CH(CH_3)_2$	

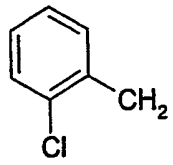
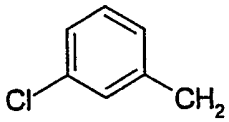
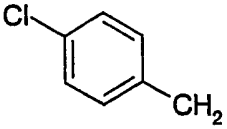
Ex No	a	b	X	R^3	R^4
96	1	3	CH_2	$CH(CH_3)_2$	
97	2	3	S	H	
98	2	4		H	
99	2	3	CH_2	H	
100	2	4		H	
101	1	3	S	H	
102	1	4		H	
103	1	3	CH_2	H	
104	1	4		H	
105	1	3	CF_2	H	
106	1	4	S	CH_3	
107	1	4		$CH(CH_3)_2$	
108	1	4	CH_2	CH_3	
109	1	4		$CH(CH_3)_2$	
110	1	3	S	$CH(CH_3)_2$	
111	1	3	CH_2	$CH(CH_3)_2$	
112	2	3	S	H	
113	2	4		H	
114	2	3	CH_2	H	
115	2	4		H	
116	1	3	S	H	
117	1	4		H	
118	1	3	CH_2	H	
119	1	4		H	
120	1	3	CF_2	H	
121	1	4		H	
122	1	4	S	CH_3	
123	1	4		$CH(CH_3)_2$	
124	1	4	CH_2	CH_3	
125	1	4		$CH(CH_3)_2$	
126	1	3	S	$CH(CH_3)_2$	
127	1	3	CH_2	$CH(CH_3)_2$	
128	2	3	S	H	

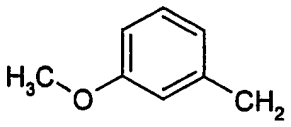
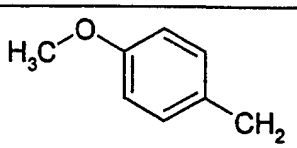
Ex No	a	b	X	R^3	R^4
129	2	4		H	
130	2	3	CH_2	H	
131	2	4		H	
132	1	3	S	H	
133	1	4		H	
134	1	3	CH_2	H	
135	1	4		H	
136	1	3	CF_2	H	
137	1	4		H	
138	1	4	S	CH_3	
139	1	4		$CH(CH_3)_2$	
140	1	4	CH_2	CH_3	
141	1	4		$CH(CH_3)_2$	
142	1	3	S	$CH(CH_3)_2$	
143	1	3	CH_2	$CH(CH_3)_2$	
144	2	3	S	H	
145	2	4		H	
146	2	3	CH_2	H	
147	2	4		H	
148	1	3	S		
149	1	4			
150	1	4	CH_2		
151	1	3	CF_2		
152	1	4			
153	1	4	S	CH_3	
154	1	4		$CH(CH_3)_2$	
155	1	4	CH_2	CH_3	
156	1	4		$CH(CH_3)_2$	
157	1	3	S	$CH(CH_3)_2$	
158	1	3	CH_2	$CH(CH_3)_2$	
159	2	3	S	H	
160	2	4		H	
161	2	3	CH_2	H	

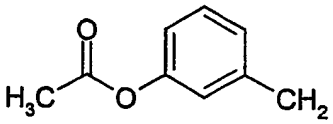
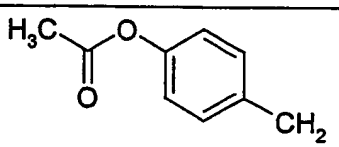
Ex No	a	b	X	R^3	R^4
162	2	4		H	
163	1	3	S	H	
164	1	4		H	
165	1	3	CH_2	H	
166	1	4		H	
167	1	3	CF_2	H	
168	1	4		H	
169	1	4	S	CH_3	
170	1	4		$CH(CH_3)_2$	
171	1	4	CH_2	CH_3	
172	1	4		$CH(CH_3)_2$	
173	1	3	S	$CH(CH_3)_2$	
174	1	3	CH_2	$CH(CH_3)_2$	
175	2	3	S	H	
176	2	4		H	
177	2	3	CH_2	H	
178	2	4		H	
179	1	3	S	H	
180	1	4		H	
181	1	3	CH_2	H	
182	1	4		H	
183	1	3	CF_2	H	
184	1	4		H	
185	1	4	S	CH_3	
186	1	4		$CH(CH_3)_2$	
187	1	4	CH_2	CH_3	
188	1	4		$CH(CH_3)_2$	
189	1	3	S	$CH(CH_3)_2$	
190	1	3	CH_2	$CH(CH_3)_2$	
191	2	3	S	H	
192	2	4		H	
193	2	3	CH_2	H	
194	2	4		H	

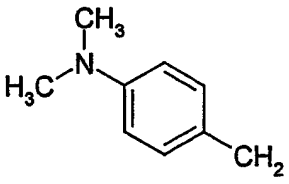
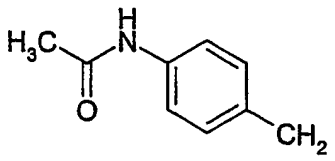
Ex No	a	b	X	R^3	R^4
195	1	3	S	H	
196	1	4		H	
197	1	3	CH_2	H	
198	1	4		H	
199	1	3	CF_2	H	
200	1	4		H	
201	1	4	S	CH_3	
202	1	4		$CH(CH_3)_2$	
203	1	4	CH_2	CH_3	
204	1	4		$CH(CH_3)_2$	
205	1	3	S	$CH(CH_3)_2$	
206	1	3	CH_2	$CH(CH_3)_2$	
207	2	3	S	H	
208	2	4		H	
209	2	3	CH_2	H	
210	2	4		H	
211	1	3	S	H	
212	1	4		H	
213	1	3	CH_2	H	
214	1	4		H	
215	1	3	CF_2	H	
216	1	4		H	
217	1	4	S	CH_3	
218	1	4		$CH(CH_3)_2$	
219	1	4	CH_2	CH_3	
220	1	4		$CH(CH_3)_2$	
221	1	3	S	$CH(CH_3)_2$	
222	1	3	CH_2	$CH(CH_3)_2$	
223	2	3	S	H	
224	2	3	CH_2	H	
225	2	4		H	
226	1	3	S	H	
227	1	4		H	

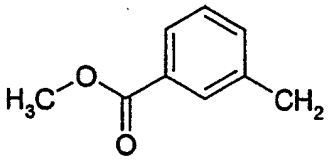
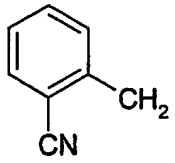
Ex No	a	b	X	R^3	R^4
228	1	3	CH_2	H	
229	1	4		H	
230	1	3	CF_2	H	
231	1	4		H	
232	1	4	S	CH_3	
233	1	4		$CH(CH_3)_2$	
234	1	4	CH_2	CH_3	
235	1	4		$CH(CH_3)_2$	
236	1	3	S	$CH(CH_3)_2$	
237	1	3	CH_2	$CH(CH_3)_2$	
238	2	3	S	H	
239	2	4		H	
240	2	3	CH_2	H	
241	2	4		H	
242	1	3	S	H	
243	1	4		H	
244	1	3	CH_2	H	
245	1	4		H	
246	1	3	CF_2	H	
247	1	4		H	
248	1	4	S	CH_3	
249	1	4		$CH(CH_3)_2$	
250	1	4	CH_2	CH_3	
251	1	4		$CH(CH_3)_2$	
252	1	3	S	$CH(CH_3)_2$	
253	1	3	CH_2	$CH(CH_3)_2$	
254	2	3	S	H	
255	2	4		H	
256	2	3	CH_2	H	
257	2	4		H	
258	1	3	S	H	
259	1	4		H	
260	1	3	CH_2	H	

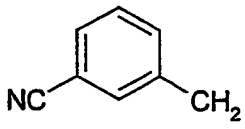
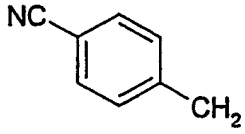
Ex No	a	b	X	R^3	R^4
261	1	4		H	
262	1	3	CF_2	H	
263	1	4		H	
264	1	4	S	CH_3	
265	1	4		$CH(CH_3)_2$	
266	1	4	CH_2	CH_3	
267	1	4		$CH(CH_3)_2$	
268	1	3	S	$CH(CH_3)_2$	
269	1	3	CH_2	$CH(CH_3)_2$	
270	2	3	S	H	
271	2	4		H	
272	2	3	CH_2	H	
273	2	4		H	
274	1	3	S	H	
275	1	4		H	
276	1	3	CH_2	H	
277	1	4		H	
278	1	3	CF_2	H	
279	1	4		H	
280	1	4	S	CH_3	
281	1	4		$CH(CH_3)_2$	
282	1	4	CH_2	CH_3	
283	1	4		$CH(CH_3)_2$	
284	1	3	S	$CH(CH_3)_2$	
285	1	3	CH_2	$CH(CH_3)_2$	
286	2	3	S	H	
287	2	4		H	
288	2	3	CH_2	H	
289	2	4		H	
290	1	3	S	H	
291	1	4		H	
292	1	3	CH_2	H	
293	1	4		H	

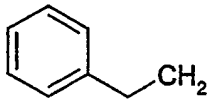
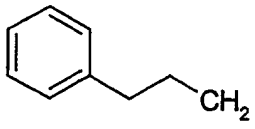
Ex No	a	b	X	R^3	R^4
294	1	3	CF_2	H	
295	1	4		H	
296	1	4	S	CH_3	
297	1	4		$CH(CH_3)_2$	
298	1	4	CH_2	CH_3	
299	1	4		$CH(CH_3)_2$	
300	1	3	S	$CH(CH_3)_2$	
301	1	3	CH_2	$CH(CH_3)_2$	
302	2	3	S	H	
303	2	4		H	
304	2	3	CH_2	H	
305	2	4		H	
306	1	3	S	H	
307	1	4		H	
308	1	3	CH_2	H	
309	1	4		H	
310	1	3	CF_2	H	
311	1	4		H	
312	1	4	S	CH_3	
313	1	4		$CH(CH_3)_2$	
314	1	4	CH_2	CH_3	
315	1	4		$CH(CH_3)_2$	
316	1	3	S	$CH(CH_3)_2$	
317	1	3	CH_2	$CH(CH_3)_2$	
318	2	3	S	H	
319	2	4		H	
320	2	3	CH_2	H	
321	2	4		H	
322	1	3	S	H	
323	1	4		H	
324	1	3	CH_2	H	
325	1	4		H	
326	1	3	CF_2	H	

Ex No	a	b	X	R^3	R^4
327	1	4		H	
328	1	4	S	CH_3	
329	1	4		$CH(CH_3)_2$	
330	1	4	CH_2	CH_3	
331	1	4		$CH(CH_3)_2$	
332	1	3	S	$CH(CH_3)_2$	
333	1	3	CH_2	$CH(CH_3)_2$	
334	2	3	S	H	
335	2	4		H	
336	2	3	CH_2	H	
337	2	4		H	
338	1	3	S	H	
339	1	4		H	
340	1	3	CH_2	H	
341	1	4		H	
342	1	3	CF_2	H	
343	1	4		H	
344	1	4	S	CH_3	
345	1	4		$CH(CH_3)_2$	
346	1	4	CH_2	CH_3	
347	1	4		$CH(CH_3)_2$	
348	1	3	S	$CH(CH_3)_2$	
349	1	3	CH_2	$CH(CH_3)_2$	
350	2	3	S	H	
351	2	4		H	
352	2	3	CH_2	H	
353	2	4		H	
354	1	3	S	H	
355	1	4		H	
356	1	3	CH_2	H	
357	1	4		H	
358	1	3	CF_2	H	
359	1	4		H	

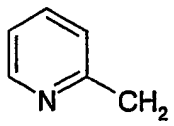
Ex No	a	b	X	R^3	R^4
360	1	4	S	CH_3	
361	1	4		$CH(CH_3)_2$	
362	1	4	CH_2	CH_3	
363	1	4		$CH(CH_3)_2$	
364	1	3	S	$CH(CH_3)_2$	
365	1	3	CH_2	$CH(CH_3)_2$	
366	2	3	S	H	
367	2	4		H	
368	2	3	CH_2	H	
369	2	4		H	
370	1	3	S	H	
371	1	4		H	
372	1	3	CH_2	H	
373	1	4		H	
374	1	3	CF_2	H	
375	1	4		H	
376	1	4	S	CH_3	
377	1	4		$CH(CH_3)_2$	
378	1	4	CH_2	CH_3	
379	1	4		$CH(CH_3)_2$	
380	1	3	S	$CH(CH_3)_2$	
381	1	3	CH_2	$CH(CH_3)_2$	
382	2	3	S	H	
383	2	4		H	
384	2	3	CH_2	H	
385	2	4		H	
386	1	3	S	H	
387	1	4		H	
388	1	3	CH_2	H	
389	1	4		H	
390	1	3	CF_2	H	
391	1	4		H	
392	1	4	S	CH_3	

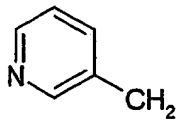
Ex No	a	b	X	R^3	R^4
393	1	4		$CH(CH_3)_2$	
394	1	4	CH_2	CH_3	
395	1	4		$CH(CH_3)_2$	
396	1	3	S	$CH(CH_3)_2$	
397	1	3	CH_2	$CH(CH_3)_2$	
398	2	3	S	H	
399	2	4		H	
400	2	3	CH_2	H	
401	2	4		H	
402	1	3	S	H	
403	1	4		H	
404	1	3	CH_2	H	
405	1	4		H	
406	1	3	CF_2	H	
407	1	4		H	
408	1	4	S	CH_3	
409	1	4		$CH(CH_3)_2$	
410	1	4	CH_2	CH_3	
411	1	4		$CH(CH_3)_2$	
412	1	3	S	$CH(CH_3)_2$	
413	1	3	CH_2	$CH(CH_3)_2$	
414	2	3	S	H	
415	2	4		H	
416	2	3	CH_2	H	
417	2	4		H	
418	1	3	S	H	
419	1	4		H	
420	1	3	CH_2	H	
421	1	4		H	
422	1	3	CF_2	H	
423	1	4		H	
424	1	4	S	CH_3	
425	1	4		$CH(CH_3)_2$	

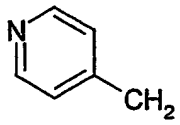
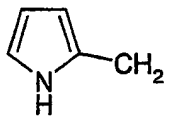
Ex No	a	b	X	R^3	R^4
426	1	4	CH_2	CH_3	
427	1	4		$CH(CH_3)_2$	
428	1	3	S	$CH(CH_3)_2$	
429	1	3	CH_2	$CH(CH_3)_2$	
450	2	3	S	H	
451	2	4		H	
452	2	3	CH_2	H	
453	2	4		H	
454	1	3	S	H	
455	1	4		H	
456	1	3	CH_2	H	
457	1	4		H	
458	1	3	CF_2	H	
459	1	4		H	
460	1	4	S	CH_3	
461	1	4		$CH(CH_3)_2$	
462	1	4	CH_2	CH_3	
463	1	4		$CH(CH_3)_2$	
464	1	3	S	$CH(CH_3)_2$	
465	1	3	CH_2	$CH(CH_3)_2$	
466	2	3	S	H	
467	2	4		H	
468	2	3	CH_2	H	
469	2	4		H	
470	1	3	S	H	
471	1	4		H	
472	1	3	CH_2	H	
473	1	4		H	
474	1	3	CF_2	H	
475	1	4		H	
476	1	4	S	CH_3	
477	1	4		$CH(CH_3)_2$	
478	1	4	CH_2	CH_3	

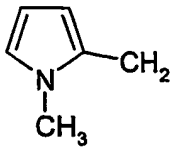
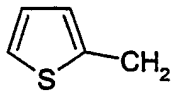
Ex No	a	b	X	R^3	R^4
479	1	4		$CH(CH_3)_2$	
480	1	3	S	$CH(CH_3)_2$	
481	1	3	CH_2	$CH(CH_3)_2$	
482	2	3	S	H	
483	2	4		H	
484	2	3	CH_2	H	
485	2	4		H	
486	1	3	S	H	
487	1	4		H	
488	1	3	CH_2	H	
489	1	4		H	
490	1	3	CF_2	H	
491	1	4		H	
492	1	4	S	CH_3	
493	1	4		$CH(CH_3)_2$	
494	1	4	CH_2	CH_3	
495	1	4		$CH(CH_3)_2$	
496	1	3	S	$CH(CH_3)_2$	
497	1	3	CH_2	$CH(CH_3)_2$	
498	2	3	S	H	
499	2	4		H	
500	2	3	CH_2	H	
501	2	4		H	
502	1	3	S	H	
503	1	4		H	
504	1	3	CH_2	H	
505	1	4		H	
506	1	3	CF_2	H	
507	1	4		H	
508	1	4	S	CH_3	
509	1	4		$CH(CH_3)_2$	
510	1	4	CH_2	CH_3	
511	1	4		$CH(CH_3)_2$	

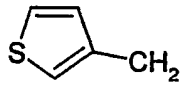
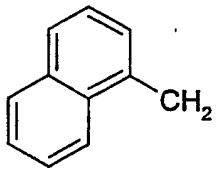
Ex No	a	b	X	R^3	R^4
512	1	3	S	$CH(CH_3)_2$	
513	1	3	CH_2	$CH(CH_3)_2$	
514	2	3	S	H	
515	2	4		H	
516	2	3	CH_2	H	
517	2	4		H	
518	1	3	S	H	
519	1	4		H	
520	1	3	CH_2	H	
521	1	4		H	
522	1	3	CF_2	H	
523	1	4		H	
524	1	4	S	CH_3	
525	1	4		$CH(CH_3)_2$	
526	1	4	CH_2	CH_3	
527	1	4		$CH(CH_3)_2$	
528	1	3	S	$CH(CH_3)_2$	
529	1	3	CH_2	$CH(CH_3)_2$	
530	2	3	S	H	
531	2	4		H	
532	2	3	CH_2	H	
533	2	4		H	
534	1	3	S	H	
535	1	4		H	
536	1	3	CH_2	H	
537	1	4		H	
538	1	3	CF_2	H	
539	1	4		H	
540	1	4	S	CH_3	
541	1	4		$CH(CH_3)_2$	
542	1	4	CH_2	CH_3	
543	1	4		$CH(CH_3)_2$	
544	1	3	S	$CH(CH_3)_2$	

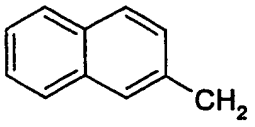
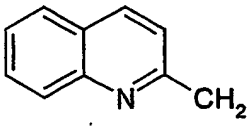


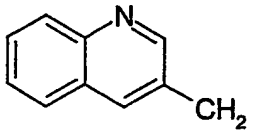
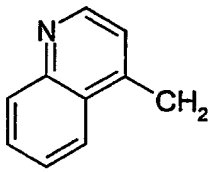
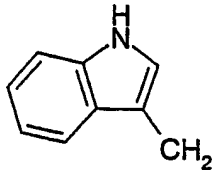


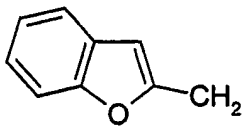
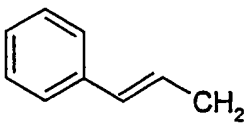
Ex No	a	b	X	R^3	R^4
545	1	3	CH_2	$CH(CH_3)_2$	
546	2	3	S	H	
547	2	4		H	
548	2	3	CH_2	H	
549	2	4		H	
550	1	3	S	H	
551	1	4		H	
552	1	3	CH_2	H	
553	1	4		H	
554	1	3	CF_2	H	
555	1	4		H	
556	1	4	S	CH_3	
557	1	4		$CH(CH_3)_2$	
558	1	4	CH_2	CH_3	
559	1	4		$CH(CH_3)_2$	
560	1	3	S	$CH(CH_3)_2$	
561	1	3	CH_2	$CH(CH_3)_2$	
562	2	3	S	H	
563	2	4		H	
564	2	3	CH_2	H	
565	2	4		H	
566	1	3	S	H	
567	1	4		H	
568	1	3	CH_2	H	
569	1	4		H	
570	1	3	CF_2	H	
571	1	4		H	
572	1	4	S	CH_3	
573	1	4		$CH(CH_3)_2$	
574	1	4	CH_2	CH_3	
575	1	4		$CH(CH_3)_2$	
576	1	3	S	$CH(CH_3)_2$	
577	1	3	CH_2	$CH(CH_3)_2$	

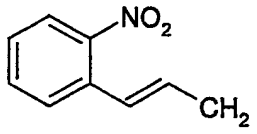
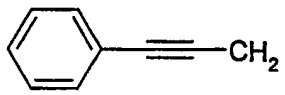
Ex No	a	b	X	R^3	R^4
578	2	3	S	H	
579	2	4		H	
580	2	3	CH_2	H	
581	2	4		H	
582	1	3	S	H	
583	1	4		H	
584	1	3	CH_2	H	
585	1	4		H	
586	1	3	CF_2	H	
587	1	4		H	
588	1	4	S	CH_3	
589	1	4		$CH(CH_3)_2$	
590	1	4	CH_2	CH_3	
591	1	4		$CH(CH_3)_2$	
592	1	3	S	$CH(CH_3)_2$	
593	1	3	CH_2	$CH(CH_3)_2$	
594	2	3	S	H	
595	2	4		H	
596	2	3	CH_2	H	
597	2	4		H	
598	1	3	S	H	
599	1	4		H	
600	1	3	CH_2	H	
601	1	4		H	
602	1	3	CF_2	H	
603	1	4		H	
604	1	4	S	CH_3	
605	1	4		$CH(CH_3)_2$	
606	1	4	CH_2	CH_3	
607	1	4		$CH(CH_3)_2$	
608	1	3	S	$CH(CH_3)_2$	
609	1	3	CH_2	$CH(CH_3)_2$	
610	2	3	S	H	

Ex No	a	b	X	R^3	R^4
611	2	4		H	
612	2	3	CH_2	H	
613	2	4		H	
614	1	3	S	H	
615	1	4		H	
616	1	3	CH_2	H	
617	1	4		H	
618	1	3	CF_2	H	
619	1	4		H	
620	1	4	S	CH_3	
621	1	4		$CH(CH_3)_2$	
622	1	4	CH_2	CH_3	
623	1	4		$CH(CH_3)_2$	
624	1	3	S	$CH(CH_3)_2$	
625	1	3	CH_2	$CH(CH_3)_2$	
626	2	3	S	H	
627	2	4		H	
628	2	3	CH_2	H	
629	2	4		H	
630	1	3	S	H	
631	1	4		H	
632	1	3	CH_2	H	
633	1	4		H	
634	1	3	CF_2	H	
635	1	4		H	
636	1	4	S	CH_3	
637	1	4		$CH(CH_3)_2$	
638	1	4	CH_2	CH_3	
639	1	4		$CH(CH_3)_2$	
640	1	3	S	$CH(CH_3)_2$	
641	1	3	CH_2	$CH(CH_3)_2$	
642	2	3	S	H	
643	2	4		H	

Ex No	a	b	X	R^3	R^4
644	2	3	CH_2	H	
645	2	4		H	
646	1	3	S	H	
647	1	4		H	
648	1	3	CH_2	H	
649	1	4		H	
650	1	3	CF_2	H	
651	1	4		H	
652	1	4	S	$CH(CH_3)_2$	
653	1	4	CH_2	CH_3	
654	1	4		$CH(CH_3)_2$	
655	1	3	S	$CH(CH_3)_2$	
656	1	3	CH_2	$CH(CH_3)_2$	
657	2	3	S	H	
658	2	4		H	
659	2	3	CH_2	H	
660	2	4		H	
661	1	3	S	H	
662	1	4		H	
663	1	3	CH_2	H	
664	1	4		H	
665	1	3	CF_2	H	
666	1	4		H	
667	1	4	S	CH_3	
668	1	4		$CH(CH_3)_2$	
669	1	4	CH_2	CH_3	
670	1	4		$CH(CH_3)_2$	
671	1	3	S	$CH(CH_3)_2$	
672	1	3	CH_2	$CH(CH_3)_2$	
673	2	3	S	H	
674	2	4		H	
675	2	3	CH_2	H	
676	2	4		H	

Ex No	a	b	X	R^3	R^4
677	1	3	S	H	
678	1	4	CH_2	H	
679	1	3	CF_2	H	
680	1	4		H	
681	1	4	S	CH_3	
682	1	4		$CH(CH_3)_2$	
683	1	4	CH_2	CH_3	
684	1	4		$CH(CH_3)_2$	
685	1	3	S	$CH(CH_3)_2$	
686	1	3	CH_2	$CH(CH_3)_2$	
687	2	3	S	H	
688	2	4	CH_2	H	
689	1	3	S	H	
690	1	4		H	
691	1	3	CH_2	H	
692	1	4		H	
693	1	3	CF_2	H	
694	1	4		H	
695	1	4	S	CH_3	
696	1	4		$CH(CH_3)_2$	
697	1	4	CH_2	CH_3	
698	1	4		$CH(CH_3)_2$	
699	1	3	S	$CH(CH_3)_2$	
700	1	3	CH_2	$CH(CH_3)_2$	
701	2	3	S	H	
702	2	4		H	
703	2	3	CH_2	H	
704	2	4		H	
705	1	3	S	H	
706	1	4		H	
707	1	3	CH_2	H	
708	1	4		H	
709	1	3	CF_2	H	

Ex No	a	b	X	R^3	R^4
710	1	4		H	
711	1	4	S	CH_3	
712	1	4		$CH(CH_3)_2$	
713	1	4	CH_2	CH_3	
714	1	4		$CH(CH_3)_2$	
715	1	3	S	$CH(CH_3)_2$	
716	1	3	CH_2	$CH(CH_3)_2$	
717	2	3	S	H	
718	2	4		H	
719	2	3	CH_2	H	
720	2	4		H	
721	1	3	S	H	
722	1	4		H	
723	1	3	CH_2	H	
724	1	4		H	
725	1	3	CF_2	H	
726	1	4		H	
727	1	4	S	CH_3	
728	1	4		$CH(CH_3)_2$	
729	1	4	CH_2	CH_3	
730	1	4		$CH(CH_3)_2$	
731	1	3	S	$CH(CH_3)_2$	
732	1	3	CH_2	$CH(CH_3)_2$	
733	2	3	S	H	
734	2	4		H	
735	2	3	CH_2	H	
736	2	4		H	
737	1	3	S	H	
738	1	3	CH_2	H	
739	1	4		H	
740	1	3	CF_2	H	
741	1	4		H	
742	1	4	S	CH_3	

Ex No	a	b	X	R^3	R^4
743	1	4		$CH(CH_3)_2$	
744	1	4	CH_2	CH_3	
745	1	4		$CH(CH_3)_2$	
746	1	3	S	$CH(CH_3)_2$	
747	1	3	CH_2	$CH(CH_3)_2$	
748	2	3	S	H	
749	2	4		H	
750	2	3	CH_2	H	
751	2	4		H	
752	1	3	S	H	
753	1	4		H	
754	1	3	CH_2	H	
755	1	4		H	
756	1	3	CF_2	H	
757	1	4		H	
758	1	4	S	CH_3	
759	1	4		$CH(CH_3)_2$	
760	1	4	CH_2	CH_3	
761	1	4		$CH(CH_3)_2$	
762	1	3	S	$CH(CH_3)_2$	
763	1	3	CH_2	$CH(CH_3)_2$	
764	2	3	S	H	
765	2	4		H	
766	2	3	CH_2	H	
767	2	4		H	
768	1	3	S	H	
769	1	4		H	
770	1	3	CH_2	H	
771	1	4		H	
772	1	3	CF_2	H	
773	1	4		H	
774	1	4	S	CH_3	
775	1	4		$CH(CH_3)_2$	

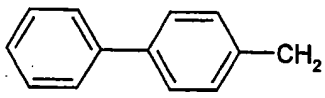
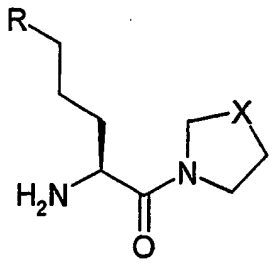
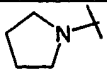
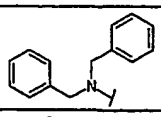
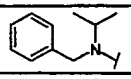
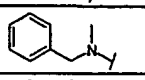
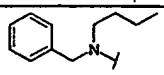
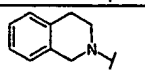
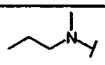
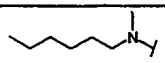
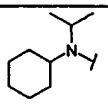
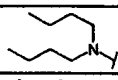
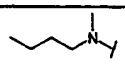
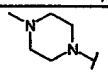
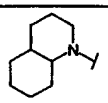
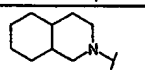
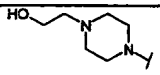
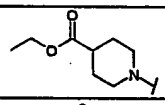
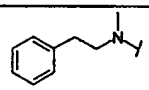
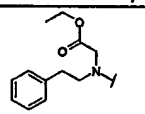
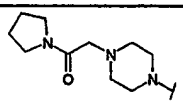
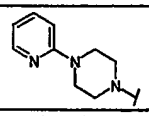
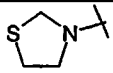
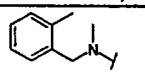
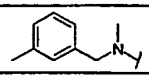
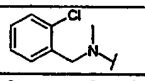
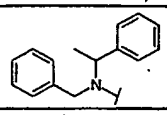
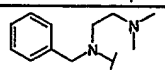
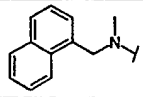
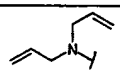
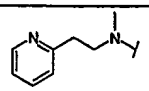
Ex No	a	b	X	R^3	R^4
776	1	4	CH_2	CH_3	
777	1	4		$CH(CH_3)_2$	
778	1	3	S	$CH(CH_3)_2$	
779	1	3	CH_2	$CH(CH_3)_2$	
780	2	3	S	H	
781	2	4		H	
782	2	3	CH_2	H	
783	2	4		H	
784	1	3	S	H	
785	1	4		H	
786	1	3	CH_2	H	
787	1	4		H	
788	1	3	CF_2	H	
789	1	4		H	
790	1	4	S	CH_3	
791	1	4		$CH(CH_3)_2$	
792	1	4	CH_2	CH_3	
793	1	4		$CH(CH_3)_2$	
794	1	3	S	$CH(CH_3)_2$	
795	1	3	CH_2	$CH(CH_3)_2$	
796	2	3	S	H	
797	2	4		H	
798	2	3	CH_2	H	
799	2	4		H	

TABLE 4



Example No	X	R	Example No	X	R
800	S		841	S	
801	CH_2		842	CH_2	
802	S		843	S	
803	CH_2		844	CH_2	
804	S		845	S	
805	CH_2		846	CH_2	
806	S		847	S	
807	CH_2			CH_2	
808	S		848	S	
809	CH_2		849	CH_2	
810	S		850	S	
811	CH_2		851	CH_2	
812	S		852	S	
813	CH_2		853	CH_2	
814	S		854	S	
815	CH_2		855	CH_2	
816	S		856	S	
817	CH_2		857	CH_2	
818	S		858	S	
819	CH_2		859	CH_2	
820	S		860	S	
821	CH_2		861	CH_2	
822	S		862	S	
823	CH_2		863	CH_2	
824	S		864	S	
825	CH_2		865	CH_2	
826	S		866	S	
827	CH_2		867	CH_2	
828	CH_2		868	S	
829			869	CH_2	
830	S		870	S	
831	CH_2		871	CH_2	

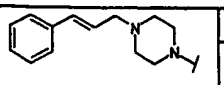
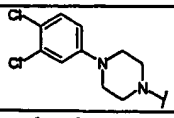
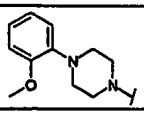
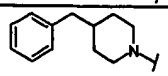
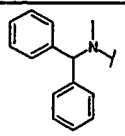
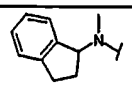
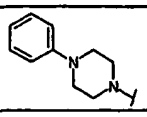
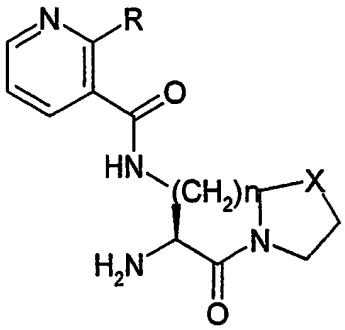
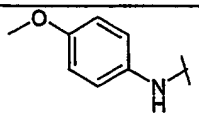
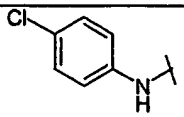
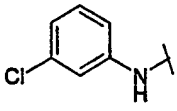
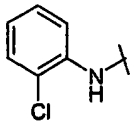
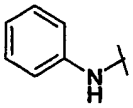
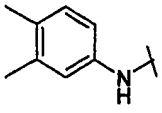
832	S		872	S	
833	CH_2		873	CH_2	
834	S		874	S	
835	CH_2		875	CH_2	
836	S		876	S	
837	CH_2		877	CH_2	
838	S				
839	CH_2				

TABLE 5



Example No	n	X	R	Example No	n	X	R
878	3	S		933	3	S	
879	4			934	4		
880	3	CH_2		935	3	CH_2	
881	4			936	4		
882	3	S		937	3	S	
883	4			938	4		
884	3	CH_2		939	3	CH_2	
885	4			940	4		
886	3	S		941	3	S	
887	4			942	4		
888	3	CH_2		943	3	CH_2	
889	4			944	4		

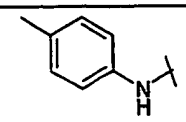
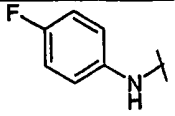
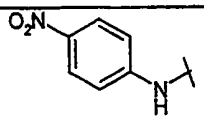
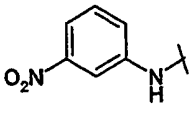
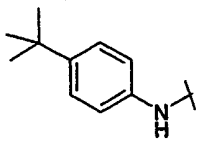
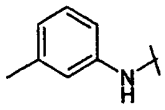
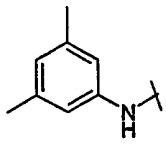
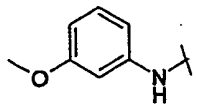
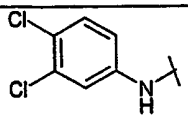
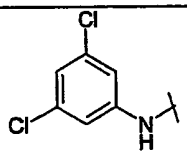
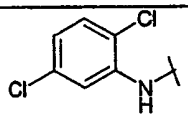
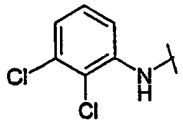
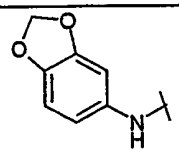
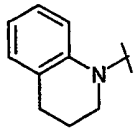
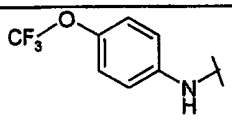
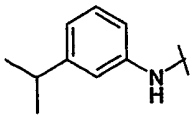
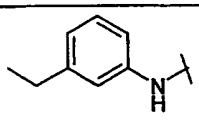
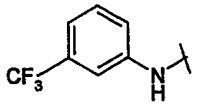
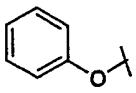
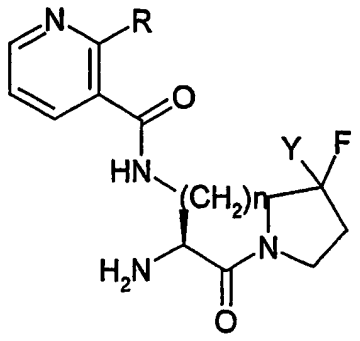
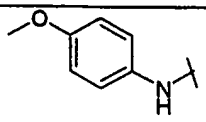
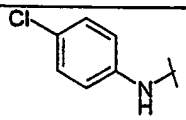
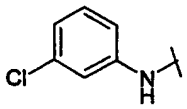
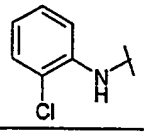
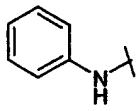
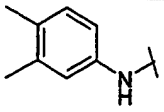
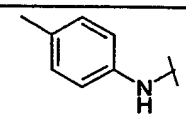
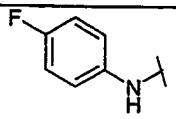
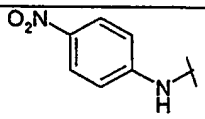
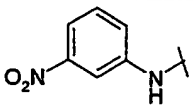
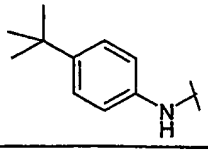
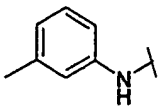
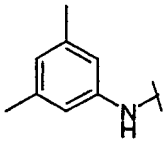
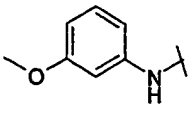
890	3	S		945	3	S	
891	4						
892	3	CH_2				CH_2	
893	4			946	4		
894	3	S		947	3	S	
895	4			948	4		
896	3	CH_2		949	3	CH_2	
897	4			950	4		
898	3	S		951	3	S	
899	4			952	4		
900	3	CH_2		953	3	CH_2	
901	4			954	4		
902	3	S		955	3	S	
903	4			956	4		
904	3	CH_2		957	3	CH_2	
905	4			958	4		
906	3	S		959	3	S	
907	4			960	4		
908	3	CH_2		961	3	CH_2	
909	4			962	4		
910	3	S		963	3	S	
911	4			964	4		
912	3	CH_2		965	3	CH_2	
913	4			966	4		
914	3	S		967	3	S	
915	4			968	4		
916	3	CH_2		969	3	CH_2	
917	4			970	4		
918	3	S		971	3	S	
919	4			972	4		
920	3	CH_2		973	3	CH_2	
0	4			974	4		
921	3	S		975	4	S	
922	4			976			
923	3	CH_2		977	3	CH_2	
924	4			978	4		
925	3	S		979	3	S	MeS
926	4			980	4		
927	3	CH_2		981	3	CH_2	
928	4			982	4		
929	3	S	Me	983	3	S	MeO
930	4			984	4		
931	3	CH_2		985	3	CH_2	
932	4			986	4		

TABLE 6



Example No	n	X	R	Example No	n	X	R
987	3	S		1044	3	S	
988	4			1045	4		
989	3	CH_2		1046	3	CH_2	
990	4			1047	4		
991	4	S		1048	3	S	
992				1049	4		
993	3	CH_2		1050	3	CH_2	
994	4			1051	4		
995	3	S		1052	3	S	
996	4			1053	4		
997	3	CH_2		1054	3	CH_2	
998	4			1055	4		
999	3	S		1056	3	S	
1000	4						
1001	3	CH_2				CH_2	
1002	4			1057	4		
1003	3	S		1058	3	S	
1004	4			1059	4		
1005	3	CH_2		1060	3	CH_2	
1006	4			1061	4		
1007	3	S		1062	3	S	
1008	4			1063	4		
1009	3	CH_2		1064	3	CH_2	
1010	4			1065	4		
1011	3	S		1066	3	S	
1012	4			1067	4		
1013	3	CH_2		1068	3	CH_2	
1014	4			1069	4		

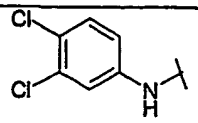
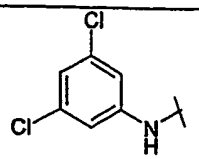
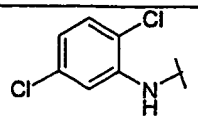
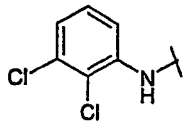
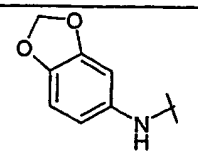
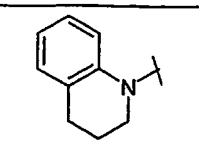
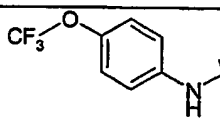
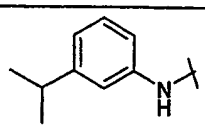
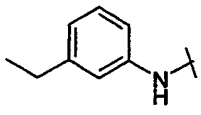
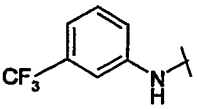
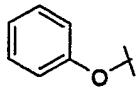
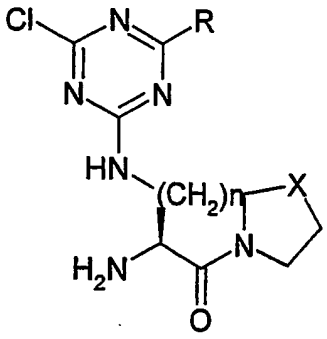
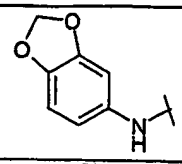
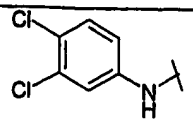
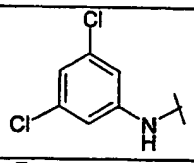
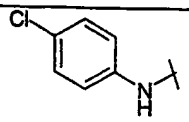
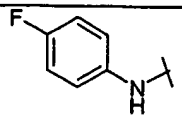
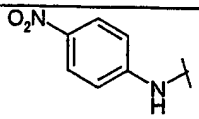
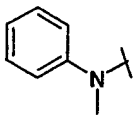
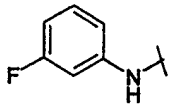
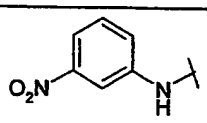
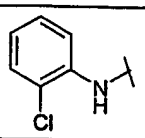
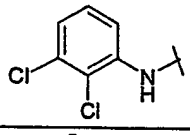
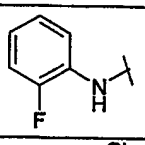
1015	3	S		1070	3	S	
1016	4			1071	4		
1017	3	CH_2		1072	3	CH_2	
1018	4			1073	4		
1019	3	S		1074	3	S	
1020	4			1075	4		
1021	3	CH_2		1076	3	CH_2	
1022	4			1077	4		
1023	3	S		1078	3	S	
1024	4			1079	4		
1025	3	CH_2		1080	3	CH_2	
1026	4			1081	4		
1027	3	S		1082	3	S	
1028	4			1083	4		
1029	3	CH_2		1084	3	CH_2	
1030	4			1085	4		
1031	3	S		1086	3	S	
1032	4			1087	4		
1033	3	CH_2		1088	3	CH_2	
1034	4			1089	4		
1035	3	S		1090	3	S	MeS
1036	4			1091	4		
1037	3	CH_2		1092	3	CH_2	
1038	4			1093	4		
1039	3	S	Me	1094	3	S	MeO
1040	4			1095	4		
1041	3	CH_2		1096	3	CH_2	
1042	4			1097	4		

TABLE 7



Example No	n	X	R	Example No	N	X	R
1098	3	S		1145	3	S	
1099	4			1146	4		
1100	3	CH_2		1147	3	CH_2	
1101	4			1148	4		
1102	3	S		1149	3	S	
1103	4			1150	4		
1104	3	CH_2		1151	3	CH_2	
1105	4			1152	4		
1106	3	S		1153	3	S	
1107	4			1154	4		
1108	3	CH_2		1155	3	CH_2	
1109	4			1156	4		
1110	3	S		1157	3	S	
1111	4						
1112	3	CH_2				CH_2	
1113	4			1158	4		
1114	3	S		1159	3	S	
1115	4			1160	4		
1116	3	CH_2		1161	3	CH_2	
1117	4			1162	4		
1118	3	S		1163	3	S	
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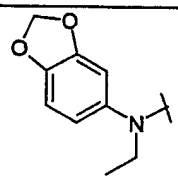
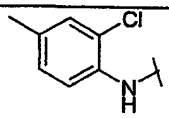
1120	3	CH_2		1165	3	CH_2	
1121	4			1166	4		
1122	3	S		1167	3	S	
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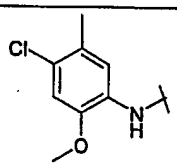
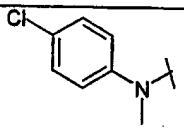
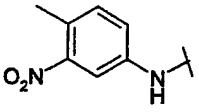
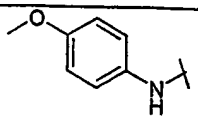
1124	3	CH_2		1169	3	CH_2	
1125	4			1170	4		
1125a	3	S		1171	3	S	
1126	4			1172	4		
1127	3	CH_2		1173	3	CH_2	
1128	4			1174	4		
1129	3	S		1175	3	S	
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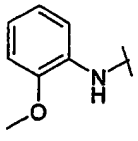
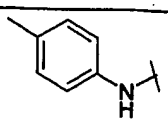
1131	3	CH_2		1177	3	CH_2	
1132	4			1178	4		
1133	3	S		1179	3	S	
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1135	3	CH_2		1181	3	CH_2	
1136	4			1182	4		

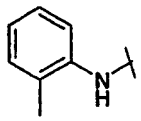
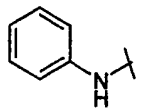
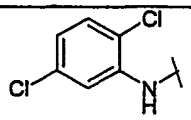
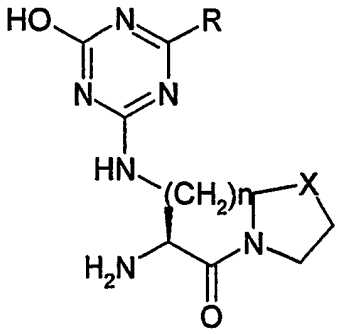
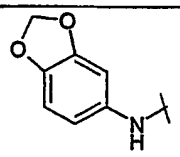
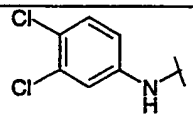
1137	3	S		1183	3	S	
1138	4			1184	4		
1139	3	CH_2		1185	3	CH_2	
1140	4			1186	4		
1141	3	S					
1142							
1143	3	CH_2					
1144	4						

TABLE 8



Example No	n	X	R	Example No	n	X	R
1187	3	S		1235	3	S	
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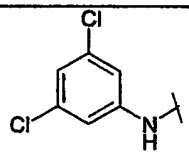
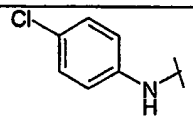
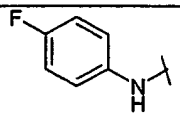
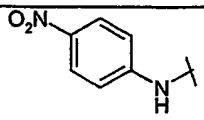
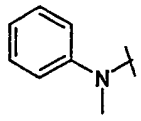
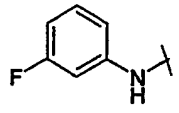
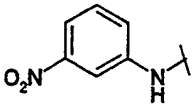
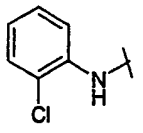
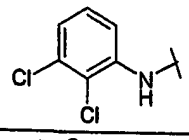
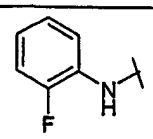
1189	3	CH_2		1237	3	CH_2	
1190	4			1238	4		
1191	3	S		1239	3	S	
1192	4			1240	4		
1193	3	CH_2		1241	3	CH_2	
1194	4			1242	4		
1195	3	S		1243	3	S	
1196	4			1244	4		
1197	3	CH_2		1245	3	CH_2	
1198	4			1246	4		
1199	3	S		1247	3	S	
1200	4						
1201	3	CH_2				CH_2	
1202	4			1248	4		
1203	3	S		1249	3	S	
1204	4			1250	4		
1205	3	CH_2		1251	3	CH_2	
1206	4			1252	4		

1207	3	S		1253	3	S	
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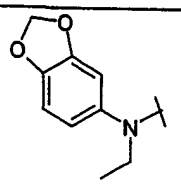
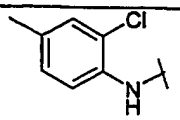
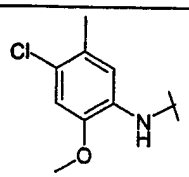
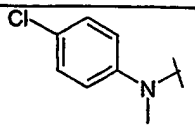
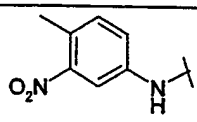
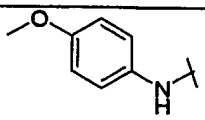
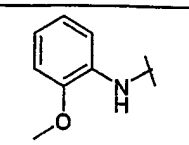
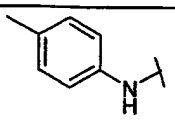
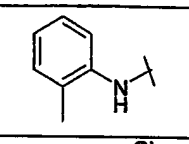
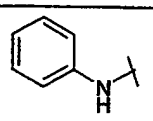
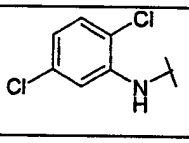
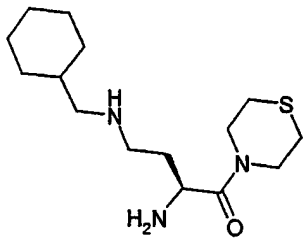
1209	3	CH_2		1255	3	CH_2	
1210	4			1256	4		
1211	3	S		1257	3	S	
1212	4			1258	4		
1213	3	CH_2		1259	3	CH_2	
1214	4			1260	4		
1215	3	S		1261	3	S	
1216	4			1262	4		
1217	3	CH_2		1263	3	CH_2	
1218	4			1264	4		
1219	3	S		1265	3	S	
1220	4			1266	4		
1221	3	CH_2		1267	3	CH_2	
1222	4			1268	4		
1223	3	S		1269	3	S	
1224	4			1270	4		
1225	3	CH_2		1271	3	CH_2	
1226	4			1272	4		
1227	3	S		1273	3	S	
1228	4			1274	4		
1229	3	CH_2		1275	3	CH_2	
1230	4			1276	4		
1231	3	S					
1232							
1233	3	CH_2					
1235	4						

EXAMPLE 1277

1-[2-(S)-Amino-4-(cyclohexylmethylamino)butanoyl]thiomorpholine dihydrochloride



A. 1-[2-(S)-N-(*tert*-Butyloxycarbonyl)amino-4-(9-fluorenylmethyloxycarbonylamino)-butanoyl]thiomorpholine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)amino-4-(9-fluorenylmethyloxycarbonylamino)-butanoic acid (1.0g, 2.27mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 20mL). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (461mg, 3.41mmol), water-soluble carbodiimide (521mg, 2.72mmol), thiomorpholine (281mg, 2.72mmol) and triethylamine (340mg, 3.4mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100mL). The solution was washed with 0.3M $KHSO_4$ (2 x 25mL), sat. $NaHCO_3$ (2 x 25mL), water (2 x 25mL) and brine (1 x 25mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a white solid identified as 1-[2-(S)-N-(*tert*-butyloxycarbonyl)amino- 4-(9-fluorenylmethyloxycarbonylamino)-butanoyl]thiomorpholine (516mg, 0.98mmol, 43%).

B. 1-[2-(S)-*N*-(*tert*-Butyloxycarbonyl)-4-amino)-butanoyl]thiomorpholine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)amino- 4-(9-fluorenylmethyloxycarbonylamino)-butanoyl thiomorpholine (500mg, 0.95mmol) was dissolved in tetrahydrofuran (20mL). Diethylamine (5mL) was added. After 90min at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 1-[2-(*S*)-N-(*tert*-butyloxycarbonyl)-4-amino)-butanoyl]thiomorpholine (162mg, 0.54mmol, 56%).

C. 1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-amino-4-(cyclohexylmethylamino)butanoyl] thiomorpholine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-4-amino)-butanoyl]thiomorpholine (41mg, 0.135mmol) was dissolved in dichloroethane (10mL). To this solution was added cyclohexanecarboxaldehyde (15mg, 0.135mmol). After 30mins sodium triacetoxyborohydride (32mg, 0.15mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid,9% methanol, 90% chloroform) to give a colourless oil identified as 1-[2-(S)-N-(*tert*-butyloxycarbonyl)-amino-4-(cyclohexylmethylamino)butanoyl] thiomorpholine (25mg, 0.063mmol, 47%).

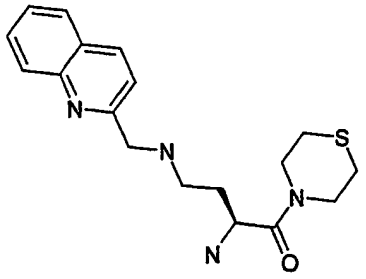
D. 1-[2-(S)-Amino-4-(cyclohexylmethylamino)butanoyl]thiomorpholine dihydrochloride

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-amino-4-(cyclohexylmethylamino)butanoyl]thiomorpholine (25mg, 0.063mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[2-(S)-amino-4-(cyclohexylmethylamino)butanoyl]thiomorpholine dihydrochloride (23mg, 0.063mmol, 100%).

$[M+H]^+ = 300.3$

EXAMPLE 1278

1-[2-(S)-Amino-4-((quinolin-2-ylmethyl)amino)butanoyl]thiomorpholine dihydrochloride



A. 1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-amino-4-((quinolin-2-ylmethyl)amino)butanoyl thiomorpholine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-4-amino)-butanoyl]thiomorpholine (41mg, 0.135mmol) was dissolved in 1,2-dichloroethane (10mL). To this solution was added 2-quinolinecarboxaldehyde (32mg, 0.15mmol). After 30mins sodium triacetoxyborohydride (36mg, 0.17mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid,9% methanol, 90% chloroform) to give a colourless oil identified as 1-[2-(S)-N-(*tert*-butyloxycarbonyl)-amino-4-((quinolin-2-ylmethyl)amino)butanoyl thiomorpholine (32mg, 0.072mmol, 53%).

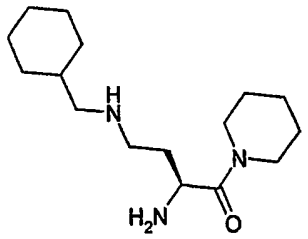
B. 1-[2-(S)-Amino-4-((quinolin-2-ylmethyl)amino)butanoyl]thiomorpholine dihydrochloride

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-amino-4-((quinolin-2-ylmethyl)amino)butanoyl] thiomorpholine (12mg, 0.027mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[2-(S)-amino-4-((quinolin-2-ylmethyl)amino)butanoyl]thiomorpholine dihydrochloride (11.3mg, 0.027mmol, 100%).

$[M+H]^+ = 345.3$

EXAMPLE 1279

1-[2-(S)-Amino-4-(cyclohexylmethylamino)butanoyl]piperidine dihydrochloride



A. 1-[2-(S)-N-(*tert*-Butyloxycarbonyl)amino-4-(9-fluorenylmethyloxycarbonylamino)-butanoyl] piperidine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)amino-4-(9-fluorenylmethyloxycarbonylamino)-butanoic acid (947mg, 2.154mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 20mL). To this

solution at 0°C were added 1-hydroxybenzotriazole hydrate (436mg, 3.2mmol), water-soluble carbodiimide (495g, 2.58mmol), piperidine (220g, 2.58mmol) and triethylamine (320mg, 3.2mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100mL). The solution was washed with 0.3M $KHSO_4$ (2 x 25mL), sat. $NaHCO_3$ (2 x 25mL), water (2 x 25mL) and brine (1 x 25mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a white solid identified as 1-[2-(S)-N-(*tert*-butyloxycarbonyl)amino- 4-(9-fluorenylmethyloxycarbonylamino)-butanoyl]piperidine (556mg, 1.1mmol, 51%).

B. 1-[2-*(S)*-*N*-(*tert*-Butyloxycarbonyl)-4-amino)-butanoyl]piperidine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)amino- 4-(9-fluorenylmethyloxycarbonylamino)-butanoyl] piperidine (540g, 1.1mmol) was dissolved in tetrahydrofuran (20mL). Diethylamine (5mL) was added. After 90min at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 1-[2-(S)-N-(*tert*-butyloxycarbonyl)-4-amino)-butanoyl] piperidine (171mg, 0.6mmol, 57%).

C. 1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-amino-4-(cyclohexylmethylamino)butanoyl] piperidine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-4-amino)-butanoyl] piperidine (43mg, 0.15mmol) was dissolved in 1,2-dichloroethane (20mL). To this solution was added cyclohexanecarboxaldehyde (17mg, 0.15mmol). After 30mins sodium triacetoxyborohydride (36mg, 0.17mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid,9% methanol, 90% chloroform) to give a colourless oil identified as 1-[2-(S)-N-(*tert*-butyloxycarbonyl)-amino-4-(cyclohexylmethylamino)butanoyl]piperidine (38mg, 0.1mmol, 66%).

D. 1-[2-(S)-Amino-4-(cyclohexylmethylamino)butanoyl] piperidine dihydrochloride

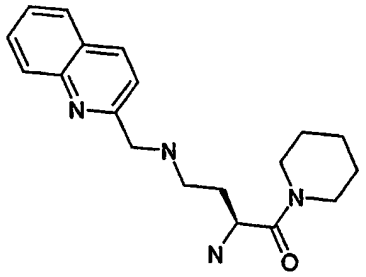
1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-amino-4-(cyclohexylmethylamino)butanoyl]piperidine (38mg, 0.1mmol) was dissolved in 4M HCl/dioxan (2mL). After 1h at room

temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[2-(S)-amino-4-(cyclohexylmethylamino)butanoyl] piperidine dihydrochloride (33mg, 0.093mmol, 93%).

$[M+H]^+ = 282.3$

EXAMPLE 1280

1-[2-(S)-Amino-4-((quinolin-2-ylmethyl)amino)butanoyl]piperidine dihydrochloride



A. 1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-amino-4-((quinolin-2-ylmethyl)amino)butanoyl] piperidine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-4-amino)-butanoyl] piperidine (24mg, 0.15mmol) was dissolved in 1,2-dichloroethane (25mL). To this solution was added 2-quinolinecarboxaldehyde (24mg, 0.15mmol). After 30mins sodium triacetoxyborohydride (36mg, 0.17mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid,9% methanol, 90% chloroform) to give a colourless oil identified as 1-[2-(S)-N-(*tert*-butyloxycarbonyl)-amino-4-((quinolin-2-ylmethyl)amino)butanoyl] piperidine (35mg, 0.082mmol, 55%).

B. 1-[2-(S)-Amino-4-((quinolin-2-ylmethyl)amino)butanoyl] piperidine dihydrochloride

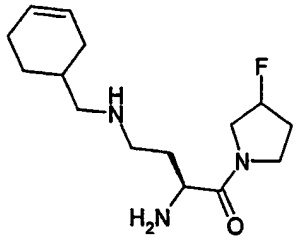
1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-amino-4-((quinolin-2-ylmethyl)amino)butanoyl] piperidine (35mg, 0.082mmol) was dissolved in 4M HCl/dioxan (2mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised

from water to give a white solid identified as 1-[2-(S)-amino-4-((quinolin-2-ylmethyl)amino)butanoyl] piperidine dihydrochloride (26mg, 0.065mmol, 79%).

$[M+H]^+ = 327.3$

EXAMPLE 1281

3-Fluoro-1-[2-(S)-amino-4-(cyclohexenylmethylamino)butanoyl]pyrrolidine dihydrochloride



A. 1-(*tert*-Butyloxycarbonyl)-3-fluoropyrrolidine

N-(*tert*-Butyloxycarbonyl)-3-hydroxypyrrolidine (21.0g, 10.7mmol) was dissolved in CH_2Cl_2 (30ml). (Diethylamino)sulphur trifluoride (1.72g, 10.7mmol) was added to this solution at -78 °C. The mixture was stirred for 18 hours at -78 °C to room temperature then the reaction mixture was carefully poured into sat. $NaHCO_3$ (100ml) and stirred for 15min and extracted with CH_2Cl_2. The organic extract was washed with water and brine, dried (Na_2SO_4) and evaporated *in vacuo* to give an orange oil. The residue was purified by flash chromatography (eluant: 28% ethyl acetate, 72% pet. ether 60-80) to give a colourless oil identified as 1-(*tert*-butyloxycarbonyl)-3-fluoropyrrolidine (1.14g, 5.34mmol, 50%).

B 3-Fluoropyrrolidine hydrochloride

1-(*tert*-Butyloxycarbonyl)-3-fluoropyrrolidine (1.14g, 5.34mmol) was dissolved in 4M HCl/dioxan (30ml). The mixture was stirred for 1 hour at room temperature then the solvent was removed *in vacuo* to give an off-white solid identified as 3-fluoropyrrolidine hydrochloride (640mg, 5.2mmol, 95%).

C. 3-Fluoro-1-[2-(S)-N-(*tert*-butyloxycarbonyl)amino-4-(9-fluorenylmethyloxycarbonylamino)-butanoyl] pyrrolidine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)amino-4-(9-fluorenylmethyloxycarbonylamino)-butanoic acid (950mg, 2.15mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 20mL). To this

solution at 0°C were added 1-hydroxybenzotriazole hydrate (395mg, 2.6mmol), water-soluble carbodiimide (572mg, 3.0mmol), 3-fluoropyrrolidine hydrochloride (270g, 2.15mmol) and triethylamine (320mg, 3.2mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100mL). The solution was washed with 0.3M $KHSO_4$ (2 x 25mL), sat. $NaHCO_3$ (2 x 25mL), water (2 x 25mL) and brine (1 x 25mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a white solid identified as 3-fluoro1-[2-(S)-N-(*tert*-butyloxycarbonyl)amino- 4-(9-fluorenylmethyloxycarbonylamino)-butanoyl]pyrrolidine (808mg, 1.58mmol, 73%).

D. 3-Fluoro-1-[2-(S)-N-(*tert*-butyloxycarbonyl)-4-amino)-butanoyl]pyrrolidine

3-Fluoro-1-[2-(S)-N-(*tert*-butyloxycarbonyl)amino- 4-(9-fluorenylmethyloxycarbonylamino)-butanoyl] pyrrolidine (800mg, 1.58mmol) was dissolved in tetrahydrofuran (20mL). Diethylamine (5mL) was added. After 90min at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 3-fluoro-1-[2-(S)-N-(*tert*-butyloxycarbonyl)-4-amino)-butanoyl] pyrrolidine (316mg, 1.04mmol, 66%).

E. 3-Fluoro-1-[2-(S)-N-(*tert*-butyloxycarbonyl)-amino-4-(cyclohexenylmethylamino)butanoyl] pyrrolidine

3-Fluoro-1-[2-(S)-N-(*tert*-butyloxycarbonyl)-4-amino)-butanoyl] pyrrolidine (150mg, 0.52mmol) was dissolved in methanol (20mL). To this solution was added 3-cyclohexenecarboxaldehyde (63mg, 0.57mmol). After 30mins sodium triacetoxyborohydride (220mg, 1.04mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid,9% methanol, 90% chloroform) to give a colourless oil identified as 3-fluoro-1-[2-(S)-N-(*tert*-butyloxycarbonyl)-amino-4-(cyclohexenylmethylamino)butanoyl]pyrrolidine (176mg, 0.46mmol, 77%).

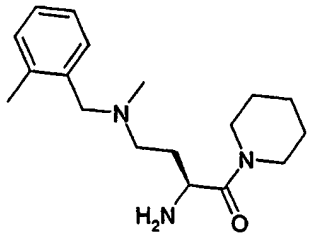
F. 3-Fluoro-1-[2-(S)-amino-4-(cyclohexenylmethylamino)butanoyl] pyrrolidine dihydrochloride

3-Fluoro-1-[2-(S)-N-(*tert*-butyloxycarbonyl)-amino-4-(cyclohexenylmethylamino)butanoyl]pyrrolidine (176mg, 0.46mmol) was dissolved in 4M HCl/dioxan (2mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 3-fluoro-1-[2-(S)-amino-4-(cyclohexenylmethylamino)butanoyl] pyrrolidine dihydrochloride (140mg, 0.39mmol, 963%).

$[M+H]^+ = 284.3$

EXAMPLE 1282

1-[2-(S)-Amino-4-(N-methyl-N-(2-methylbenzyl)amino)butanoyl]piperidine dihydrochloride



A. N-(tert-Butyloxycarbonyl)–L-homoserine lactone

L-Homoserine lactone 1.76g, 12.8mmol) was dissolved in DMF (30 mL). This solution was cooled to 0 ^{0}C, triethylamine (1.41, 14.1 mmol) di-tert-butyl dicarbonate(3.35g, 15.35 mmol) was added. After 18 hours at room temperature the solvent was evaporated *in vacuo*, the residue was taken up in dichloromethane (200 mL). This solution was washed with 1M $KHSO_4$ (2 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a white solid, recrystallised from EtOAc/pet.ether to give a white solid identified as *N*-(*tert*-butyloxycarbonyl)–L-homoserine lactone (2.25mg, 11.2mmol, 87%).

B. 1-[2-(S)-(*N*-(*tert*-Butyloxycarbonyl)amino)-4-hydroxybutanoyl]piperidine

N-(*tert*-Butyloxycarbonyl)–L-homoserine lactone (100mg, 0.5mmol) was dissolved in tetrahydrofuran (30 mL). Piperidine (42mg, 0.5mmol) was added. After 72 hours at

room temperature the reaction mixture was diluted with ethyl acetate (150 mL). This solution was washed with water (1 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil identified as 1-[2-(S)-(*N*-(*tert*-butyloxycarbonyl)amino)-4-hydroxybutanoyl]piperidine (142mg, 0.5mmol, 100%).

C. 1-[2-(S)-(*N*-(*tert*-Butyloxycarbonyl)amino)-4-oxobutanoyl] piperidine

1-[2-(S)-(*N*-(*tert*-Butyloxycarbonyl)amino)-4-hydroxybutanoyl] piperidine (142mg, 0.5mmol) was dissolved in dichloromethane (50 mL). Dess-Martin periodinane (232mg, 0.5mmol) was added. After 1 hour at room temperature the reaction mixture was diluted with ethyl acetate (150 mL). This solution was washed with water (1 x 20ml) and brine (1 x 20ml), dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil. Purified by flash chromatography on silica gel (eluant: 50% ethyl acetate, 50% pet. ether 60-80) to give a colourless oil identified as 1-[2-(S)-(*N*-(*tert*-butyloxycarbonyl)amino)-4-oxobutanoyl] piperidine (40mg, 0.14mmol, 27%).

D. 1-[2-(S)-(*N* -(*tert*-butyloxycarbonyl)amino-4-(N-methyl-N-(2-methylbenzyl)amino) butanoyl]piperidine

1-[2-(S)-(*N*-(*tert*-Butyloxycarbonyl)amino)-4-oxobutanoyl] piperidine (40mg, 14mmol) was dissolved in methanol (20mL). To this solution was added N-methyl-2-methylbenzylamine (19mg, 0.14mmol). After 2 hours sodium triacetoxyborohydride (64mg, 0.3mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel to give a colourless oil identified as 1-[2-(S)-(*N* -(*tert*-butyloxycarbonyl)amino-4-(N-methyl-N-(2-methylbenzyl)amino) butanoyl] piperidine (36mg, 0.09mmol, 64%).

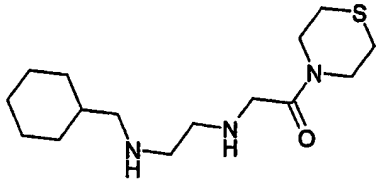
E. 1-[2-(S)-Amino-4-(N-methyl-N-(2-methylbenzyl)amino)butanoyl] piperidine dihydrochloride

1-[2-(S)-(*N*-(*tert*-Butyloxycarbonyl)amino-4-(N-methyl-N-(2-methylbenzyl)amino) butanoyl] piperidine (36mg, 0.09mmol)was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a pale brown solid identified as 1-[2-(S)-amino-4-(N-

methyl-N-(2-methylbenzyl)amino)butanoyl] piperidine dihydrochloride (43mg, 0.09mmol, 100%)

EXAMPLE 1283

1-[N-(2``-(Cyclohexylmethylaminoethyl)glycinyl)]thiomorpholine dihydrochloride



A. 1-[N-2`-(*tert*-Butyloxycarbonyl)-N-(2``-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycinyl]thiomorpholine

N-2`-(*tert*-Butyloxycarbonyl)-N-(2``-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycine (2.5g, 5.7mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 100mL). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (833mg, 6.3mmol), water-soluble carbodiimide (974mg, 6.3mmol), thiomorpholine (617mg, 6.0mmol) and N-methylmorpholine (800mg, 8mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100mL). The solution was washed with 0.3M $KHSO_4$ (2 x 25mL), sat. $NaHCO_3$ (2 x 25mL), water (2 x 25mL) and brine (1 x 25mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a white solid identified as 1-[N-2`-(*tert*-butyloxycarbonyl)-N-(2``-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycinyl]thiomorpholine (2.7g, 5.1mmol, 90%).

B. 1-[N-2`-(*tert*-Butyloxycarbonyl)-(2``-aminoethyl)-glycinyl] thiomorpholine

1-[N-2`-(*tert*-Butyloxycarbonyl)-N-(2``-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycinyl]thiomorpholine (2.7g, 5.1mmol) was dissolved in tetrahydrofuran (20mL). Diethylamine (5mL) was added. After 90min at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 1-[N-2`-(*tert*-butyloxycarbonyl)-(2``-aminoethyl)-glycinyl] thiomorpholine (1.44g, 4.7mmol, 92%).

C. 1-[2`-N-(*tert*-Butyloxycarbonyl *N*-(2``-(cyclohexylmethylaminoethyl)-glycinyl] thiomorpholine

1-[N-2`-(*tert*-Butyloxycarbonyl)-(2``-aminoethyl)-glycinyl] thiomorpholine (100mg, 0.3mmol) was dissolved in methanol (25mL). To this solution was added cyclohexanecarboxaldehyde (34mg, 0.3mmol). After 30mins sodium triacetoxyborohydride (126mg, 0.6mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid,9% methanol, 90% chloroform) to give a colourless oil identified as 1-[2`-N-(*tert*-Butyloxycarbonyl *N*-(2``-(cyclohexylmethylaminoethyl)-glycinyl] thiomorpholine (33mg, 0.08mmol, 27%).

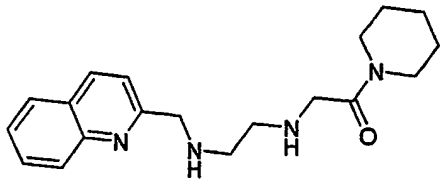
D. 1-[N-(2``-(Cyclohexylmethylaminoethyl)glycinyl)]thiomorpholine dihydrochloride

1-[2`-N-(*tert*-Butyloxycarbonyl-*N*-(2``-(cyclohexylmethylaminoethyl)-glycinyl] thiomorpholine (33mg, 0.081mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[N-(2``-(cyclohexylmethylaminoethyl)glycinyl)]thiomorpholine dihydrochloride (31mg, 0.08mmol, 100%).

$[M+H]^+ = 300.3$

EXAMPLE 1284

1-[N-(2``-((Quinolin-2-ylmethyl)aminoethyl)glycinyl)]pyrrolidine dihydrochloride



A. 1-[N-2`-(*tert*-Butyloxycarbonyl)-N-(2``-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycinyl]piperidine

N-2`-(*tert*-Butyloxycarbonyl)-N-(2``-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycine (2.5g, 5.7mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 100mL). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (1.5g, 11.1mmol), water-soluble carbodiimide (1.3g, 6.8mmol), piperidine (484mg, 5.69mmol) and N-methylmorpholine (800mg, 8mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100mL). The solution was washed with 0.3M $KHSO_4$ (2 x 25mL), sat. $NaHCO_3$ (2 x 25mL), water (2 x 25mL) and brine (1 x 25mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a white solid identified as 1-[N-2`-(*tert*-butyloxycarbonyl)-N-(2``-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycinyl]piperidine (2.8g, 5.5mmol, 96%).

B. 1-[N-2`-(*tert*-Butyloxycarbonyl)-(2``-aminoethyl)-glycinyl] piperidine

1-[N-2`-(*tert*-Butyloxycarbonyl)-N-(2``-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycinyl]piperidine (2.8g, 5.5mmol) was dissolved in tetrahydrofuran (20mL). Diethylamine (5mL) was added. After 90min at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 1-[N-2`-(*tert*-butyloxycarbonyl)-(2``-aminoethyl)-glycinyl] piperidine (1.4g, 4.9mmol, 89%).

C. 1-[2`-N-(*tert*-Butyloxycarbonyl *N*-(2``-((quinolin-2-ylmethyl)aminoethyl)-glycinyl] piperidine

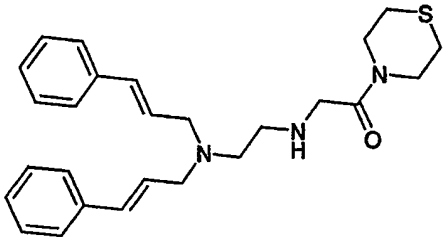
1-[N-2`-(*tert*-Butyloxycarbonyl)-(2``-aminoethyl)-glycinyl] piperidine was dissolved in methanol (25mL). To this solution was added 2-quinolinecarboxaldehyde. After 30mins sodium triacetoxyborohydride was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid,9% methanol, 90% chloroform) to give a colourless oil identified as 1-[2`-N-(*tert*-butyloxycarbonyl *N*-(2``-((quinolin-2-ylmethyl)aminoethyl)-glycinyl] piperidine.

D. 1-[N-(2``-((Quinolin-2-ylmethyl)aminoethyl)glycinyl)]piperidine dihydrochloride

1-[2`-N-(*tert*-Butyloxycarbonyl-*N*-(2``-((quinolin-2-ylmethyl)aminoethyl)-glycinyl] piperidine was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[N-(2``-((quinolin-2-ylmethyl)aminoethyl)glycinyl)]piperidine dihydrochloride.

EXAMPLE 1285

1-[N,N-(2``,2``-((Dicinnamyl)aminoethyl)glycinyl)]thiomorpholine dihydrochloride



A. 1-[2`-N-(*tert*-Butyloxycarbonyl N,N-(2``,2``-((dicinnamyl)aminoethyl)-glycinyl] thiomorpholine

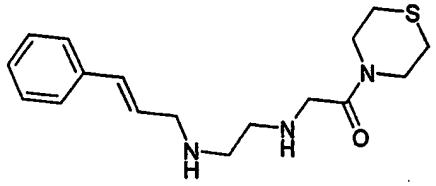
(2*S*)-1-(*N*$^{\alpha}$-(*tert*-Butyloxycarbonyl)-L-lysinyl)-pyrrolidine-2-carbonitrile (250mg, 0.83mmol) was dissolved in dichloroethane (25mL). To this solution was added trans-cinnamaldehyde (108mg, 0.83mmol). After 30mins sodium triacetoxyborohydride (350mg, 1. 6mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 2% methanol, 98% chloroform) to give a colourless oil identified as 1-[2`-N-(*tert*-butyloxycarbonyl N,N-(2``,2``-((dicinnamyl)aminoethyl)-glycinyl] thiomorpholine. Further elution with 9% methanol, 90% chloroform and 1% acetic acid gave a colourless oil identified as 1-[2`-N-(*tert*-butyloxycarbonyl N,-(2``-((cinnamyl)aminoethyl)-glycinyl] thiomorpholine (180mg, 0.43mmol, 52%)

B. 1-[N,N-(2``,2``-((Dicinnamyl)aminoethyl)glycinyl)]thiomorpholine dihydrochloride

1-[2`-N-(*tert*-Butyloxycarbonyl N,N-(2``,2``-((dicinnamyl)aminoethyl)-glycinyl] thiomorpholine was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[N,N-(2``,2``-((dicinnamyl)aminoethyl)glycinyl)]thiomorpholine dihydrochloride.

EXAMPLE 1286

1-[N-(2``-((Cinnamyl)aminoethyl)glycinyl)]thiomorpholine dihydrochloride



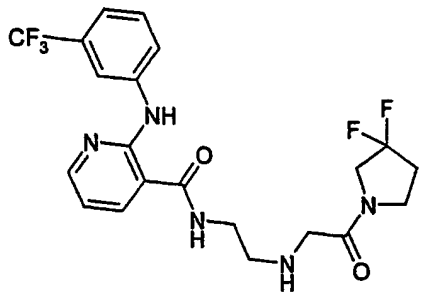
A. 1-[N-(2``-((Cinnamyl)aminoethyl)glycinyl)]thiomorpholine dihydrochloride

1-[2`-N-(*tert*-Butyloxycarbonyl N-(2``-((cinnamyl)aminoethyl)-glycinyl] thiomorpholine (180mg, 0.43mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[N-(2``-((cinnamyl)aminoethyl)glycinyl)]thiomorpholine dihydrochloride (168mg, 0.43mmol, 100%).

$[M+H]^+ = 320.3$

EXAMPLE 1287

3,3-Difluoro-1-[*N*-2``-(3'-trifluoromethylanilino)pyridyl-3-carbonyl aminoethyl)glycinyl)]pyrrolidine dihydrochloride



A. 3,3-Difluoro-1-[N-2`-(*tert*-butyloxycarbonyl)-N-(2``-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycinyl] pyrrolidine

N-2`-(*tert*-Butyloxycarbonyl)-N-(2``-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycine (1.0g, 2.27mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 100mL). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (620mg, 4.6mmol), water-soluble carbodiimide (560mg, 2.8mmol), 3,3-difluoropyrrolidine hydrochloride (360mg, 2.5mmol) and N-methylmorpholine (800mg, 8mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100mL). The solution was washed with 0.3M $KHSO_4$ (2 x 25mL), sat. $NaHCO_3$ (2 x 25mL), water (2 x 25mL) and brine (1 x 25mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 60% ethyl acetate, 40% pet. ether) to give a white solid identified as 3,3-difluoro-1-[N-2`-(*tert*-butyloxycarbonyl)-N-(2``-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycinyl] pyrrolidine (934g, 1.7mmol, 77%).

B.3,3-Difluoro-1-[N-2`-(*tert*-butyloxycarbonyl)aminoethyl)-glycinyl] pyrrolidine

3,3-Difluoro-1-[N-2`-(*tert*-butyloxycarbonyl)-N-(2``-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycinyl] pyrrolidine (890g, 1.68mmol) was dissolved in tetrahydrofuran (20mL). Diethylamine (5mL) was added. After 90min at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 3,3-difluoro-1-[N-2`-(*tert*-butyloxycarbonyl)aminoethyl)-glycinyl] pyrrolidine (470mg, 1.5mmol, 91%).

C. 3,3-Difluoro-1-[N-2`-(*tert*-butyloxycarbonyl)-*N*-2``-(3'-trifluoromethylanilino)pyridyl-3-carbonyl aminoethyl)glycinyl)]pyrrolidine

3,3-Difluoro-1-[N-2`-(*tert*-butyloxycarbonyl)aminoethyl)-glycinyl] pyrrolidine (50mg, 0.16mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 20mL). To this solution at 0°C was

added 1-hydroxybenzotriazole hydrate (46mg, 0.34mmol), water-soluble carbodiimide (40mg, 0.2mmol), niflumic acid (49mg, 0.17mmol) and N-methylmorpholine (40mg, 0.4mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (70mL). The solution was washed with 0.3M $KHSO_4$ (1 x 20mL), sat. $NaHCO_3$ (1 x 20mL), water (1 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a yellow oil identified as 3,3-difluoro-1-[N-2`-(*tert*-butyloxycarbonyl)-*N*-2``-(3'-trifluoromethylanilino)pyridyl-3-carbonyl aminoethyl)glycinyl)]pyrrolidine (63mg, 0.11mmol, 67%).

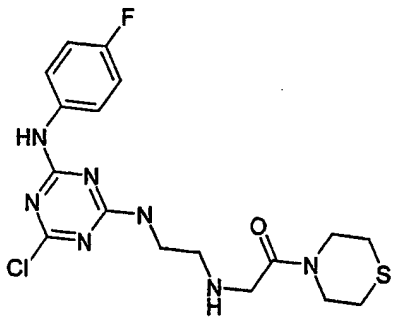
D. 3,3-Difluoro-1-[*N*-2``-(3'-trifluoromethylanilino)pyridyl-3-carbonyl aminoethyl) glycinyl)]pyrrolidine dihydrochloride

3,3-Difluoro-1-[N-2`-(*tert*-butyloxycarbonyl)-*N*-2``-(3'-trifluoromethylanilino)pyridyl-3-carbonyl aminoethyl)glycinyl)]pyrrolidine (55mg, 0.10mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a pale brown solid identified as 3,3-difluoro-1-[*N*-2``-(3'-trifluoromethylanilino)pyridyl-3-carbonyl aminoethyl)glycinyl)]pyrrolidine dihydrochloride (52mg, 0.10mmol, 100%).

$[M+H]^+ = 472.3$

EXAMPLE 1288

3,3-Difluoro-[*N*-2``-(6-Chloro-4-(4'-fluoroanilino)-1,3,5-triazinyl)aminoethyl) glycinyl)]thiomorpholine dihydrochloride



A. 4,6-Dichloro-2-(4'-fluoroanilino)-1,3,5-triazine

Cyanuric chloride (1.844g, 10mmol) was dissolved in acetonitrile (20mL). The solution was cooled to –20 ^{0}C. A solution of 4-fluoroaniline (1.1g, 10mmol) and triethylamine (1.0g, 10mmol) was slowly added. After 1 hour at –20 ^{0}C the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (150mL). The solution was washed with water (1 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was recrystallised from ethyl acetate/ hexane to give an off white solid identified as 4,6-dichloro-2-(4'-fluoroanilino)-1,3,5-triazine 1.7g, 6.0mmol, 60%).

B. 1-[N-2`-(*tert*-butyloxycarbonyl)-*N*-2``- (6-Chloro-4-(4'-fluoroanilino)-1,3,5-triazinyl aminoethyl)glycinyl)] thiomorpholine

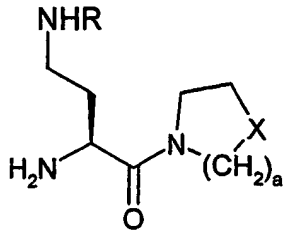
1-[N-2`-(*tert*-butyloxycarbonyl)aminoethyl)-glycinyl] thiomorpholine (100mg, 0.3mmol) was dissolved in dichloromethane (30mL). To this solution was added 4,6-dichloro-2-(4'-fluoroanilino)-1,3,5-triazine (90mg, 0.3mmol) and triethylamine (50mg, 0.5mmol). After 2 hours at room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (150mL). This solution was washed with water (2 x 30mL) and brine (1 x 30mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography (eluant: 60% ethyl acetate, 40% pet. ether) to give a white solid identified as 1-[N-2`-(*tert*-butyloxycarbonyl)-*N*-2``- (6-chloro-4-(4'-fluoroanilino)-1,3,5-triazinyl aminoethyl)glycinyl)] thiomorpholine (20mg, 0.032mmol, 11%).

C. 1-[*N*-2``-(6-Chloro-4-(4'-fluoroanilino)-1,3,5-triazinyl)aminoethyl) glycinyl)] thiomorpholine dihydrochloride

1-[N-2`-(*tert*-butyloxycarbonyl)-*N*-2``- (6-chloro-4-(4'-fluoroanilino)-1,3,5-triazinyl aminoethyl)glycinyl)] thiomorpholine (18.8mg, 0.03mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[*N*-2``-(6-Chloro-4-(4'-fluoroanilino)-1,3,5-triazinyl)aminoethyl) glycinyl)] thiomorpholine dihydrochloride (18mg, 0.03mmol, 100%).

$[M+H]^+$ = 526.4

TABLE 9



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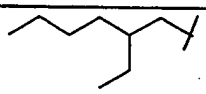
1295	S	1	
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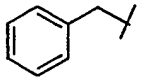
1311	S	1	
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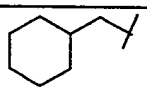
1317	S	1	
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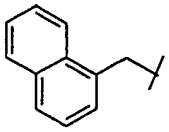
1321	S	1	
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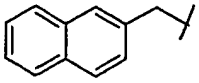
1327	S	1	
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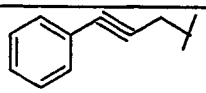
1334	CF_2		
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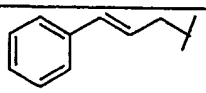
1339	S	1	
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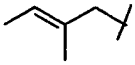
1345	S	1	
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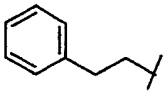
1351	S	1	
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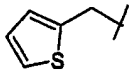
1357	S	1	
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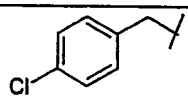
1363	S	1	
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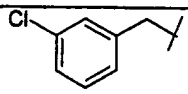
1369	S	1	
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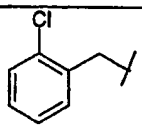
1375	S	1	
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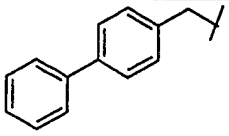
1387	S	1	
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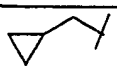
1393	S	1	
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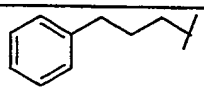
1399	S	1	
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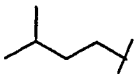
1405	S	1	
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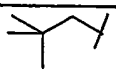
1411	S	1	
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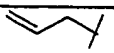
1417	S	1	
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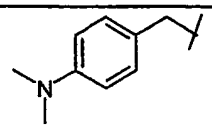
1426	S	2	
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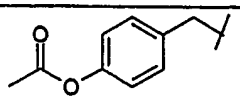
1429	S	1	
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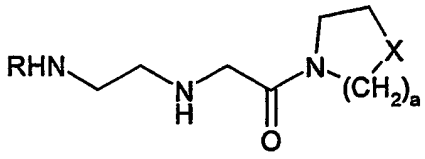
TABLE 10



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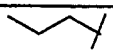
1614	S	1	
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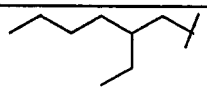
1618	S	1	
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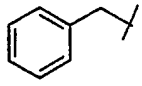
1622	S	1	
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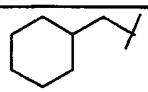
1626	S	1	
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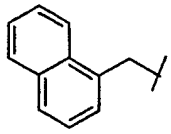
1630	S	1	
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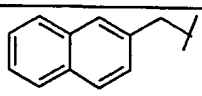
1634	S	1	
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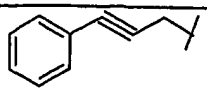
1639	CF_2		
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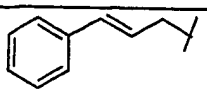
1642	S	1	
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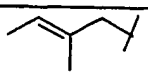
1646	S	1	
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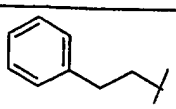
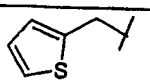
1650	S	1	
1651	CF_2		
1652	S	2	
1653	CH_2		
1654	S	1	
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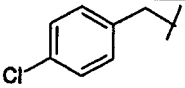
1656	S	2	
1657	CH_2		
1658	S	1	
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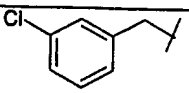
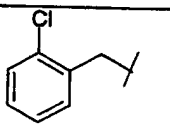
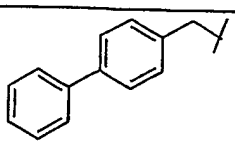
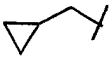
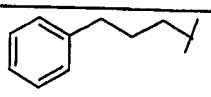
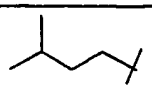
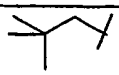
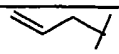
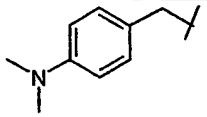
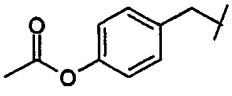
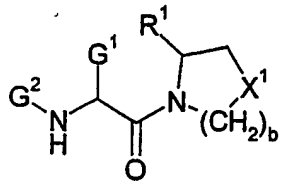
1660	S	2	
1661	CH_2		
1662	S	1	
1663	CF_2		
1664	S	2	
1665	CH_2		
1666	S	1	
1667	CF_2		
1668	S	2	
1669	CH_2		
1670	S	1	
1671	CF_2		
1672	S	2	
1673	CH_2		
1674	S	1	
1675	CF_2		
1676	S	2	
1677	CH_2		
1678	S	1	
1679	CF_2		
1680	S	2	
1681	CH_2		
1682	S	1	
1683	CF_2		
1684	S	2	

1685	CH_2		
1686	S	1	
1687	CF_2		
1688	S	2	
1689	CH_2		
1690	S	1	
1691	CF_2		
1692	S	2	
1693	CH_2		
1694	S	1	
1695	CF_2		
1696	S	2	
1697	CH_2		
1698	S	1	
1699	CF_2		
1700	S	2	
1701	CH_2		
1702	S	1	
1703	CF_2		
1704	S	2	
1705	CH_2		

CLAIMS

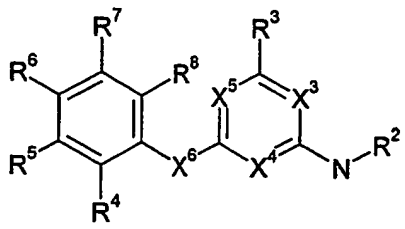
1 A compound according to general formula **1**, or a pharmaceutically acceptable salt thereof,



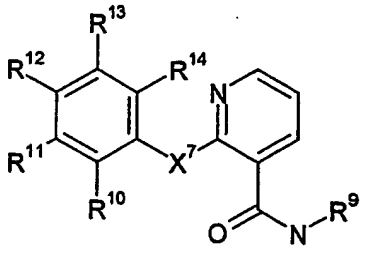
1

wherein:

either G^1 is $-CH_2-X^2-(CH_2)_a-G^3$ and G^2 is H, or
G^2 is $-CH_2-(CH_2)_a-G^3$ and G^1 is H;
G^3 is selected from a group according to general formula **2**, a group according to general formula **3**, and a group according to general formula **4**;



2



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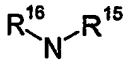


4

a is **0**, 1 or 2;
b is 1 or 2;
X^1 is selected from CH_2, S, CF_2, CHF, $CH(CH_3)$, $C(CH_3)_2$, CH(CN) and O;
X^2 is selected from CH_2, O and S, provided that if a is 1 then X^2 is CH_2;
X^3, X^4 and X^5 are selected from N and CH, provided that at least two of X^3, X^4 and X^5 are N;
X^6 is selected from O and NH;
X^7 is selected from CH_2, O, S and NH;
R^1 is selected from H and CN;

R^2 is selected from H and alkyl;

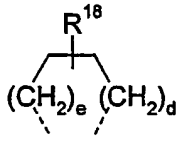
R^3 is selected from H, Cl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;

R^4, R^5, R^6, R^7 and R^8 are independently selected from H, Br, Cl, F, CF_3, alkyl, acyl, OH, O-alkyl, NH_2, NH-alkyl, $N(alkyl)_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$ and CN;

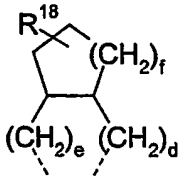
R^9 is selected from H and alkyl;

R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are independently selected from H, Br, Cl, F, CF_3, alkyl, acyl, OH, O-alkyl, NH_2, NH-alkyl, $N(alkyl)_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$ and CN;

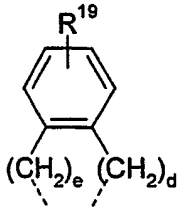
R^{15} and R^{16} are independently selected from H, alkyl, alkenyl, polyfluoroalkyl, aralkyl, aryl and $-CH_2$-L-R^{17}, or R^{15} and R^{16} together form a group according to general formula **5**, general formula **6** or general formula **7**;



5



6



7

R^{17} is selected from H, alkyl and aryl;

R^{18} is selected from H, alkyl, aryl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;

R^{19} is selected from H, alkyl, aryl, F, Cl, Br, CF_3, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;

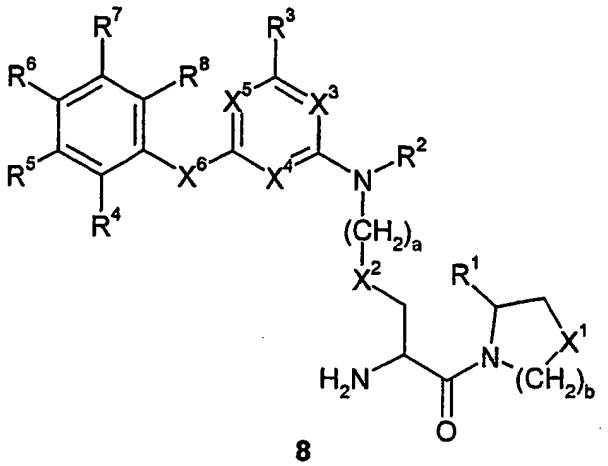
L is selected from a covalent bond, CH=CH, C≡C and $-C_6H_4-$;

d and e are selected from 0, 1, 2 and 3 such that d+e is 3, 4 or 5; and

f is selected from 1, 2 and 3;

provided that when R^{15} and R^{16} are both H and b is 1 then X^1 is not S or CH_2.

2 A compound according to general formula **8**, or a pharmaceutically acceptable salt thereof,



8

wherein:

a is **0**, 1 or 2;
b is 1 or 2;
X^1 is selected from CH_2, S, CF_2, CHF, $CH(CH_3)$, $C(CH_3)_2$, CH(CN) and O;
X^2 is selected from CH_2, O and S, provided that if a is 1 then X^2 is CH_2;
X^3, X^4 and X^5 are selected from N and CH, provided that at least two of X^3, X^4 and X^5 are N;
X^6 is selected from O and NH;
R^1 is selected from H and CN;
R^2 is selected from H and alkyl;
R^3 is selected from H, Cl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;
R^4, R^5, R^6, R^7 and R^8 are independently selected from H, Br, Cl, F, CF_3, alkyl, acyl, OH, O-alkyl, NH_2, NH-alkyl, $N(alkyl)_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$ and CN.

3 A compound according to Claim 2 wherein R^1 is H.

4 A compound according to Claim 2 wherein R^1 is CN.

5 A compound according to any of Claims 2 to 4 wherein X^1 is CH_2.

6 A compound according to any of Claims 2 to 4 wherein X^1 is S.

7 A compound according to any of Claims 2 to 6 wherein b is 1.

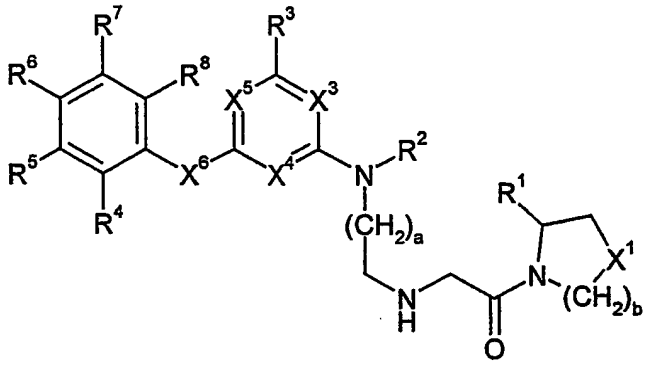
8 A compound according to any of Claims 2 to 6 wherein b is 2.

9 A compound according to any of Claims 2 to 8 wherein a is 1.

10 A compound according to any of Claims 2 to 8 wherein a is 2 and X^2 is CH_2.

11 A compound according to any of Claims 2 to 10 wherein X^3, X^4 and X^5 are all N.

12 A compound according to general formula **9**, or a pharmaceutically acceptable salt thereof,



9

wherein:

a is 1 or 2;

b is 1 or 2;

X^1 is selected from CH_2, S, CF_2, CHF, $CH(CH_3)$, $C(CH_3)_2$, CH(CN) and O;

X^3, X^4 and X^5 are selected from N and CH, provided that at least two of X^3, X^4 and X^5 are N;

X^6 is selected from O and NH;

R^1 is selected from H and CN;

R^2 is selected from H and alkyl;

R^3 is selected from H, Cl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;

R^4, R^5, R^6, R^7 and R^8 are independently selected from H, Br, Cl, F, CF_3, alkyl,

acyl, OH, O-alkyl, NH_2, NH-alkyl, N(alkyl)$_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, CON(alkyl)$_2$ and CN.

13 A compound according to Claim 12 wherein R^1 is H.

14 A compound according to Claim 12 wherein R^1 is CN.

15 A compound according to any of Claims 12 to 14 wherein X^1 is CH_2.

16 A compound according to any of Claims 12 to 14 wherein X^1 is S.

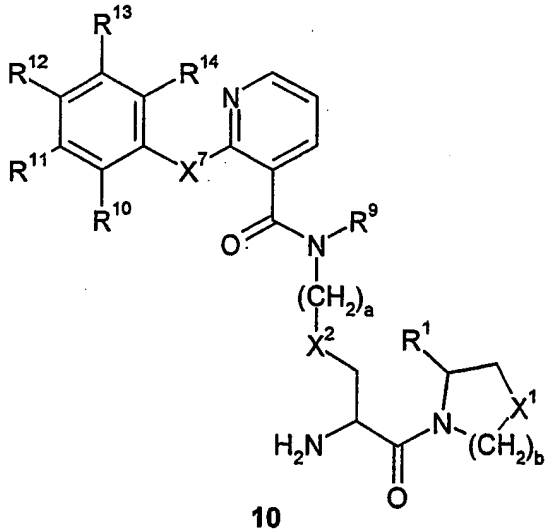
17 A compound according to any of Claims 12 to 16 wherein b is 1.

18 A compound according to any of Claims 12 to 16 wherein b is 2.

19 A compound according to any of Claims 12 to 18 wherein a is 1.

20 A compound according to any of Claims 12 to 19 wherein X^3, X^4 and X^5 are all N.

21 A compound according to general formula **10**, or a pharmaceutically acceptable salt thereof,



10

wherein:

a is **0**, 1 or 2;
b is 1 or 2;
X^1 is selected from CH_2, S, CF_2, CHF, $CH(CH_3)$, $C(CH_3)_2$, CH(CN) and O;
X^2 is selected from CH_2, O and S, provided that if a is 1 then X^2 is CH_2;
X^7 is selected from O, S, CH_2 and NH;
R^1 is selected from H and CN;
R^9 is selected from H and alkyl;
R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are independently selected from H, Br, Cl, F, CF_3, alkyl, acyl, OH, O-alkyl, NH_2, NH-alkyl, $N(alkyl)_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$ and CN is selected from H, Cl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$.

22 A compound according to Claim 21 wherein R^1 is H.

23 A compound according to Claim 21 wherein R^1 is CN.

24 A compound according to any of Claims 21 to 23 wherein X^1 is CH_2.

25 A compound according to any of Claims 21 to 23 wherein X^1 is S.

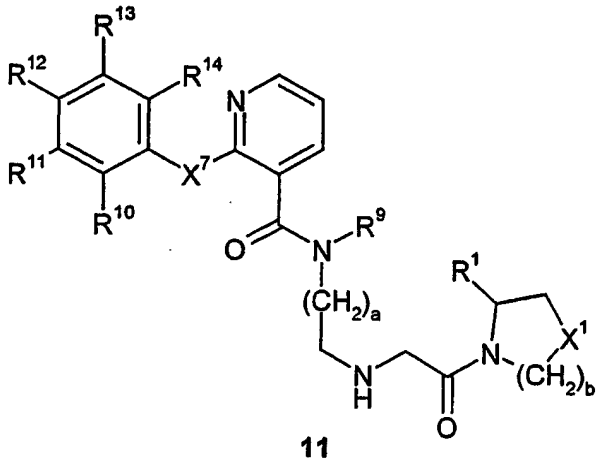
26 A compound according to any of Claims 21 to 25 wherein b is 1.

27 A compound according to any of Claims 21 to 25 wherein b is 2.

28 A compound according to any of Claims 21 to 27 wherein a is 1.

29 A compound according to any of Claims 21 to 27 wherein a is 2 and X^2 is CH_2.

30 A compound according to general formula **11**, or a pharmaceutically acceptable salt thereof,



11

wherein:

a is 1 or 2;

b is 1 or 2;

X^1 is selected from CH_2, S, CF_2, CHF, $CH(CH_3)$, $C(CH_3)_2$, CH(CN) and O;

X^7 is selected from O, S, CH_2 and NH;

R^1 is selected from H and CN;

R^9 is selected from H and alkyl;

R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are independently selected from H, Br, Cl, F, CF_3, alkyl, acyl, OH, O-alkyl, NH_2, NH-alkyl, $N(alkyl)_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$ and CN is selected from H, Cl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$.

31 A compound according to Claim 30 wherein R^1 is H.

32 A compound according to Claim 30 wherein R^1 is CN.

33 A compound according to any of Claims 30 to 32 wherein X^1 is CH_2.

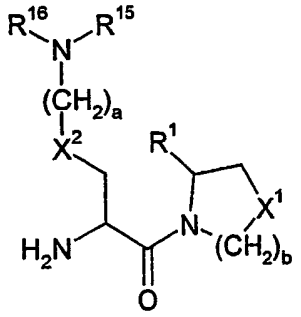
34 A compound according to any of Claims 30 to 32 wherein X^1 is S.

35 A compound according to any of Claims 30 to 34 wherein b is 1.

36 A compound according to any of Claims 30 to 34 wherein b is 2.

37 A compound according to any of Claims 30 to 36 wherein a is 1.

38 A compound according to general formula **12**, or a pharmaceutically acceptable salt thereof,



12

wherein:

a is 0, 1 or 2;

b is 1 or 2;

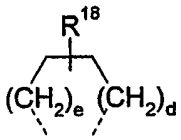
X^1 is selected from CH_2, S, CF_2, CHF, $CH(CH_3)$, $C(CH_3)_2$, CH(CN) and O;

X^2 is selected from CH_2, O and S, provided that if a is 1 then X^2 is CH_2;

R^1 is selected from H and CN;

R^{15} and R^{16} are each independently selected from H, alkyl, alkenyl, polyfluoroalkyl, aralkyl, aryl and CH_2-L-R^{17};

or R^{15} and R^{16} together are a group according to general formula 5, a group according to general formula 6 or a group according to general formula **7**;



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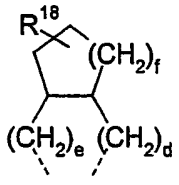

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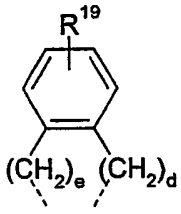


7

R^{17} is selected from H, alkyl and aryl;

R^{18} is selected from H, alkyl, aryl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;

R^{19} is selected from H, alkyl, aryl, F, Cl, Br, CF_3, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;

L is selected from a covalent bond, CH=CH, C≡C and $-C_6H_4-$;

d and e are selected from 0, 1, 2 and 3 such that d+e is 3, 4 or 5; and
f is selected from 1, 2 and 3;
provided that when R^{15} and R^{16} are both H and b is 1 then X^1 is not S or CH_2.

39 A compound according to Claim 38 wherein R^1 is H.

40 A compound according to Claim 38 wherein R^1 is CN.

41 A compound according to any of Claims 38 to 40 wherein X^1 is CH_2.

42 A compound according to any of Claims 38 to 40 wherein X^1 is S.

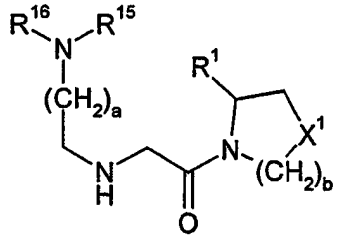
43 A compound according to any of Claims 38 to 42 wherein b is 1.

44 A compound according to any of Claims 38 to 42 wherein b is 2.

45 A compound according to any of Claims 38 to 44 wherein a is 1.

46 A compound according to any of Claims 38 to 44 wherein a is 2 and X^2 is CH_2.

47 A compound according to general formula **13**, or a pharmaceutically acceptable salt thereof,

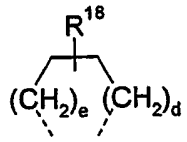


13

wherein:

a is 1 or 2;
b is 1 or 2;

X^1 is selected from CH_2, S, CF_2, CHF, $CH(CH_3)$, $C(CH_3)_2$, CH(CN) and O;
R^1 is selected from H and CN;
R^{15} and R^{16} are each independently selected from H, alkyl, alkenyl, polyfluoroalkyl, aralkyl, aryl and CH_2-L-R^{17};
or R^{15} and R^{16} together are a group according to general formula 5, a group according to general formula 6 or a group according to general formula 7;



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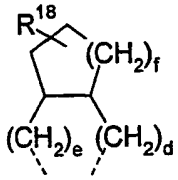
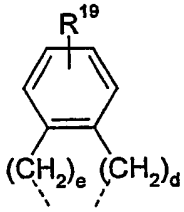


6



7

R^{17} is selected from H, alkyl and aryl;
R^{18} is selected from H, alkyl, aryl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;
R^{19} is selected from H, alkyl, aryl, F, Cl, Br, CF_3, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;
L is selected from a covalent bond, CH=CH, C≡C and -C_6H_4-;
d and e are selected from 0, 1, 2 and 3 such that d+e is 3, 4 or 5; and
f is selected from 1, 2 and 3.

48 A compound according to Claim 47 wherein R^1 is H.

49 A compound according to Claim 47 wherein R^1 is CN.

50 A compound according to any of Claims 47 to 49 wherein X^1 is CH_2.

51 A compound according to any of Claims 47 to 49 wherein X^1 is S.

52 A compound according to any of Claims 47 to 51 wherein b is 1.

53 A compound according to any of Claims 47 to 51 wherein b is 2.

54 A compound according to any of Claims 47 to 53 wherein a is 1.

55 A pharmaceutical composition comprising a compound according to any of

Claims 1 to 54.

56 A use for a compound according to any of Claims 1 to 54, which is as a component in the preparation of a pharmaceutical composition.

57 A method of treatment of disease in a human or animal subject, comprising a step of administering to the subject a therapeutically active amount of a compound according to any of Claims 1 to 54

58 A method of treatment according to claim 57 where the disease is caused by dysregulation of a post-proline cleaving proteases or their endogenous substrates.

59 A method of treatment according to claim 57 where the disease is ameliorated by inhibition of a post-proline cleaving proteases.

60 A method of treatment according to claim 57 where the disease is caused by dysregulation of a post-proline cleaving proteases or its endogenous substrates which is an intracellular protease.

61 A composition according to claim 1 or 38 with the proviso that when X^1 = S; b = 1; R^1 = H; G^2 = H; G^1 is $-CH_2-X^2-(CH_2)_a-G^3$; a = 1, $X^2 = CH_2$; $G^3 = NR^{15}R^{16}$; and one of R^{15}, R^{16} = H, the other of R^{15}, R^{16} is not pyridyl, substituted pyridyl, pyrazinyl or substituted pyrazinyl.

62 A composition according to claim 1, 38, 47 or 61 with the proviso that when b=1, R^1 is H and X^1 is S; G^1 = H; G^2 is $-CH_2-(CH_2)_a-G^3$; a = 1; G^3 is $NR^{15}R^{16}$ and one of R^{15} and R^{16} is H the other of R^{15}, R^{16} is not pyridyl, substituted pyridyl, pyrazinyl or substituted pyrazinyl.

63 A composition according to claim 1, 38, 47, 61 or 62 with the proviso that when b=1, R^1 is CN and X^1 is CH_2; G^1 = H; G^2 is $-CH_2-(CH_2)_a-G^3$; a = 1; G^3 is $NR^{15}R^{16}$ and one of R^{15} and R^{16} is H, the other of R^{15}, R^{16} is not pyridyl, substituted pyridyl, pyrazinyl or substituted pyrazinyl.

64 A composition according to claim 1, 38, 47, 61, 62 or 63 with the proviso that when G^2 = H; G^1 = -CH2-X^2-$(CH_2)_a$-G^3; X^2 is CH_2; a = 1; G3 = $NR^{15}R^{16}$ and R^{15} = R^{16} = H; b is not 2 when X^1 is O or CH_2, and b is not 1 when X^1 is CH_2.

65 A method of treatment according to claim 57 in which the disease is caused by dysregulation of a non-membrane associated post-proline cleaving proteases such as QPP, DPP-8 and DPP-9 enzymes or their endogenous substrates.

66 A method of treatment according to claim 57 in which the disease is ameliorated by inhibition of a non-membrane associated post-proline cleaving proteases such as QPP, DPP-8 and DPP-9 enzymes or their endogenous substrates.

67 A method according to claim 65 or 66 in which the compound is a selective inhibitor of non-membrane associated post-proline cleaving proteases.

INTERNATIONAL SEARCH REPORT

International Application No
PCT 02/04764

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/40 C07D207/16 C07D277/04 C07D295/18 C07D207/10
C07D417/12 C07D401/12 C07D409/12 C07D403/12 C07D405/12
A61K31/426 A61K31/427 A61K31/53 A61K31/54 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 011 155 A (VILLHAUER EDWIN BERNARD) 4 January 2000 (2000-01-04) cited in the application column 1 -column 2 examples 35,63 -----	1-37, 55-67

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 December 2002	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kollmannsberger, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte ial application No.
T/GB 02/04764

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 57-60, 65-67 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1 (partly); 2-37; 55-67 (partly)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1 (partly); 2-37; 55-67 (partly)

   Glycine substituted saturated N-containing heterocycles as defined in claim 1, substituted via a methylene containing chain by nitrogen bound biaryl moieties (defined as structures 2 or 3), corresponding compositions and uses

2. Claims: 1 (partly); 38-46; 55-60 (partly); 61; 62-67 (partly)

   Glycine substituted saturated N-containing heterocycles as defined in claim 1, substituted via a methylene containing chain by nitrogen bound substituents (defined as structure 4) in position G1 with G2=H, corresponding compositions and uses

3. Claims: 1 (partly); 47-54; 55-60 (partly); 62-67 (partly)

   Glycine substituted saturated N-containing heterocycles as defined in claim 1, substituted via a methylene containing chain by nitrogen bound substituents (defined as structure 4) in position G2 with G1=H, corresponding compositions and uses

INTERNATIONAL SEARCH REPORT

ation on patent family members

International Application No
PCT/ 02/04764

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6011155 A	04-01-2000	US 6124305 A	26-09-2000